Ovarian Cancers: Evolving Paradigms in Research and Care

DETAILS

396 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-38046-1 | DOI: 10.17226/21841

AUTHORS

Committee on the State of the Science in Ovarian Cancer Research; Board on Health Care Services; Institute of Medicine; National Academies of Sciences, Engineering, and Medicine

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Institute of Medicine

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by Contract No. 200-2011-38807 with the Centers for Disease Control and Prevention. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-38046-1
International Standard Book Number-10: 0-309-38046-4
Library of Congress Control Number: 2016933599
Digital Object Identifier: 10.17226/21841

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2016. *Ovarian cancers: Evolving paradigms in research and care*. Washington, DC: The National Academies Press. doi: 10.17226/21841.

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SHELLEY S. TWOROGER, Associate Professor of Medicine and Epidemiology, Harvard Medical School/Harvard T.H. Chan School of Public Health/Brigham and Women's Hospital

Study Staff

TRACY A. LUSTIG, Study Director
MARK D. STEWART, Research Associate
SAPANA R. VORA, Christine Mirzayan Science and Technology Policy Graduate Fellow[1]; Research Associate[2]
NOA L. NIR, Senior Program Assistant
SHARYL J. NASS, Director, Board on Health Care Services; Director, National Cancer Policy Forum

[1]January 2015 through April 2015.
[2]April 2015 through August 2015.

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

MICHAEL A. BOOKMAN, Arizona Oncology
ROBERT E. BRISTOW, University of California, Irvine
SETSUKO K. CHAMBERS, University of Arizona
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JOE GRAY, Oregon Health & Science University
TAMARA A. HENRY, The George Washington University
GEOFFREY KIM, U.S. Food and Drug Administration
ANN KOLKER, Ovarian Cancer National Alliance (retired)
GUILLERMINA LOZANO, The University of Texas MD Anderson Cancer Center
DAVID J. MOONEY, Harvard University
DARWIN J. PROCKOP, Texas A&M University Health Science Center

JOELLEN M. SCHILDKRAUT, University of Virginia School of Medicine
REBECCA SUTPHEN, University of South Florida Morsani College of Medicine; InformedDNA
NICOLE URBAN, Fred Hutchinson Cancer Research Center

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **OLUFUNMILAYO F. OLOPADE,** The University of Chicago, and **ELI Y. ADASHI,** The Warren Alpert Medical School, Brown University. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

This congressionally mandated report, sponsored by the Centers for Disease Control and Prevention, assesses the state of research on ovarian cancers from multiple perspectives, and by multiple disciplines. The report has its origins in the Gynecologic Cancer Education and Awareness Act, more commonly known as Johanna's Law, signed into law by President George W. Bush on January 12, 2007. It was named for Johanna Silver Gordon, a school teacher who died of ovarian cancer.

The findings of the committee are based on its internal expertise and input from external experts representing multiple domains of cancer research and cancer care (e.g., ovarian cancer researchers; clinicians who counsel and treat women with risk of ovarian cancer or with an ovarian cancer diagnosis; funding agencies, both governmental and private; advocacy groups; and of course women who have the disease and their families). The scientific evidence supporting the conclusions and recommendations is presented in a series of chapters that are sequenced to follow the cancer care continuum. The chapters emphasize key new information and highlight unmet needs that are unique to cancers of the ovary and their disease trajectories.

An overarching conclusion is that ovarian cancer is not one disease. There are a number of different tumor types with characteristic histologic features, distinctive molecular signatures, and disease trajectories. Moreover, these tumors are heterogeneous, and they can arise from different tissues of the female reproductive tract. Although the report touches on a number of the different ovarian cancer types, its main focus is on the most common and most lethal type, high-grade serous carcinoma.

This report is particularly timely because of the emergence of new concepts regarding the nature and origin of ovarian cancers. These new concepts have profound implications for the taxonomy of ovarian cancers; the interpretation of older literature that failed to make distinctions among ovarian cancer types; the identification of risk factors for specific ovarian cancer types; opportunities for improved early detection, prevention, and targeted molecular treatments; and the design of clinical trials. For example, the discovery that many high-grade serous ovarian carcinomas arise from a small population of cells in the distal end of the fallopian tubes, rather than the ovary per se, at once reveals the challenges of improving existing early detection and screening methods and focuses attention on potential new approaches to sampling the site of origin to identify precancerous lesions in women at risk for ovarian cancer. Additionally, these new concepts expose deficiencies in our knowledge, such as the need to identify factors that allow cells exfoliated from the tubes or other tissues of the reproductive tract to engraft and proliferate in the ovaries, as well as other common sites of metastasis. Importantly, these concepts inform potential prevention strategies for high-risk individuals, such as salpingectomy.

The 5-year survival of women with the most common and fatal type of ovarian cancer, high-grade serous carcinoma, has increased over the past four decades as a result of advances in specialty care and the development of effective first-line chemotherapy (i.e., platinum compounds in combination with drugs of the taxane family). However, there are concerning racial disparities and a number of unresolved issues regarding the optimal treatment of newly diagnosed women, which if addressed could lead to further reductions in morbidity and mortality. Moreover, important discoveries that directly influence clinical recommendations or care have not been widely adopted. For example, the recognition that a significant number of high-grade serous carcinomas arise in women harboring germline mutations in the *BRCA1* or *BRCA2* genes allows for genetic testing in families, risk prediction, and prevention interventions. Despite this important discovery of a major ovarian cancer risk factor, genetic testing and counseling for families at risk has not been universally adopted. The reasons underlying the lack of uptake remain to be determined.

The committee noted that the research agenda for ovarian cancers needs to be all encompassing given the disease trajectories. Although the most common and fatal ovarian cancers often respond initially to surgical cytoreduction and chemotherapy, they usually recur as a result of the development of resistance to existing chemotherapy drugs. The committee identified a need for social and behavioral research to improve the quality of life of survivors, research on palliative and end-of-life care, in addition to research on new primary therapies and methods to prevent the development of chemoresistance.

While pointing out these unmet research needs, the committee recognized that ovarian cancer clinical researchers face unique challenges because the disease is relatively rare among gynecologic malignancies. This relative rarity focused attention on the need to develop new clinical trial designs that are information rich in terms of molecular characterization and metadata so that clinically useful conclusions can be drawn quickly from smaller study enrollments.

In its evaluation of the state of research and promising opportunities emerging from the new understanding of the pathobiology of cancers of the ovary, the committee concluded that there is a need for research on and development of more effective dissemination strategies, that can inform diverse audiences, so that advances in the understanding of risk factors for all populations, new approaches for screening and early detection, information on optimal treatment regimens and new therapeutics, and ways to improve quality of life and end-of-life care are known by women, their health care providers, and those responsible for carrying out and sponsoring basic, translational, clinical, and comparative effectiveness research.

Jerome F. Strauss III, *Chair*
Committee on the State of the Science in Ovarian Cancer Research

Acknowledgments

The Committee on the State of the Science in Ovarian Cancer Research benefited from the contributions of many individuals. The committee takes this opportunity to recognize those who so generously gave their time and expertise to inform its deliberations.

This report was sponsored by the Centers for Disease Control and Prevention. We wish to thank Greta Massetti, Lisa Richardson, David Serwitz, Cheryll Thomas, and Tailee Tucker.

The committee benefited from presentations made by a number of experts outside the committee. The following individuals shared their experiences and perspectives during public meetings of the committee:

Calaneet Balas, *Ovarian Cancer National Alliance*
Christine Berg, *Johns Hopkins Medicine*
Ronny Drapkin, *University of Pennsylvania*
Karen Emmons, *Kaiser Permanente*
Simon Gayther, *University of Southern California*
Tony Ho, *AstraZeneca*
Melinda Irwin, *Yale University*
Guillermina Lozano, *The University of Texas MD Anderson Cancer Research Center*
Susan Lutgendorf, *University of Iowa*
Martin McIntosh, *Fred Hutchinson Cancer Research Center*
Alexander Nikitin, *Cornell University*
Nicolas Wentzensen, *National Cancer Institute*
Lari Wenzel, *University of California, Irvine*

The committee commissioned a paper to provide background information for its deliberations and to synthesize the evidence on particular issues. We thank the following individuals for their contributions to this paper:

Carolyn Lefkowits, *University of Colorado*
Rachel Ruskin, *University of Oklahoma Health Sciences Center*

We extend special thanks to the following individuals who were additional sources of information, generously giving their time and knowledge to further the committee's efforts:

Mary Eiken, *Society of Gynecologic Oncology*
Rachel Gandell, *American Congress of Obstetricians and Gynecologists*
Shannon Hawkins, *Indiana University*
Elise Kohn, *National Cancer Institute*
Laura Koontz, *Ovarian Cancer National Alliance*
Percy Ivy, *National Cancer Institute*
Debbie Miller, *Ovarian Cancer Trial Awareness Network & Empowerment*
Patricia Modrow, *U.S. Department of Defense Ovarian Cancer Research Program*
Britton Trabert, *National Cancer Institute*

Finally, many within the National Academies of Sciences, Engineering, and Medicine were helpful to the study staff. The staff would like to thank Erin Balogh, Daniel Bearss, Patrick Burke, Chelsea Frakes, Greta Gorman, Jim Jensen, Nicole Joy, Linda Kilroy, Leslie Kwan, Katye Magee, Fariha Mahmud, Sandra McDermin, Janice Mehler, Rebecca Morgan, Bettina Ritter, and Jennifer Walsh. We also thank Heather Phillips and Robert Pool, copyeditors.

Contents

Summary

Although recent years have seen many promising advances in cancer research, there remain surprising gaps in the fundamental knowledge about and understanding of ovarian cancer. Researchers now know that ovarian cancer cannot be categorized as a single disease; several distinct subtypes exist with different origins, risk factors, genetic mutations, biological behaviors, and prognoses. However, researchers do not have definitive knowledge of how and where these various ovarian cancers arise. Such unanswered questions impede progress in the prevention, early detection, treatment, and management of ovarian cancers. In particular, the failure to improve ovarian cancer morbidity and mortality during the past several decades is likely due to several factors, including

- A lack of research focusing on specific disease subtypes;
- An incomplete understanding of genetic and nongenetic risk factors;
- An inability to develop and validate effective screening and early detection tools;
- Inconsistency in the delivery of the standard of care;
- Limited precision medicine approaches tailored to the disease subtypes and tumor characteristics; and
- Limited attention paid to research on survivorship issues, including supportive care with long-term management of active disease.

The symptoms of ovarian cancers can be nonspecific, so they are often not seen as indicating a serious illness by women or their health care providers until the symptoms worsen, at which point the cancer is often

widespread and difficult to cure. Late diagnosis is a major factor contributing to the high mortality rate. Indeed, roughly two-thirds of women with ovarian cancer are diagnosed with an advanced-stage cancer (or a cancer that has not been thoroughly staged), which is associated with less than 30 percent overall 5-year survival. Furthermore, although many ovarian cancers initially respond to treatment, the vast majority recur. Recurrent ovarian cancers may respond to further treatment, but virtually all of them will ultimately become resistant to current drug therapies. Overall, little attention has been paid to managing the acute and long-term physical and psychosocial effects of ovarian cancer diagnosis and treatment or understanding when to transition to appropriate end-of-life care.

This report gives a broad overview of the state of the science in ovarian cancer research, highlights major knowledge gaps, and provides recommendations to help reduce the incidence of and morbidity and mortality from ovarian cancers by focusing on promising research themes that could advance risk prediction, prevention, early detection, comprehensive care (e.g., treatment and supportive care), and cure.

STUDY CONTEXT, CHARGE, AND APPROACH

Although ovarian cancer is relatively uncommon, it is one of the deadliest cancers. Each year in the United States, more than 21,000 women are diagnosed with ovarian cancer, and more than 14,000 women die from the disease. Ovarian cancer is the fifth leading cause of cancer deaths among American women, and the 5-year survival rate is just under 46 percent. By contrast, the 5-year survival rate is nearly 90 percent for breast cancer, more than 80 percent for endometrial cancer, and nearly 70 percent for cervical cancer. Indeed, although the estimated number of new cases of ovarian cancer among American women each year is only one-tenth the number of new cases of breast cancer, the death-to-incidence ratio for ovarian cancer is more than three times higher than that for breast cancer (see Figure S-1).

Ovarian cancer has been called a "silent killer" because no distinctive symptoms had been associated with the early stages of the disease. However, recent research shows that most women with ovarian cancer report symptoms such as bloating, pelvic or abdominal pain, and urinary symptoms, and many women recall having had these symptoms for an extended period of time before diagnosis. In 2006, the U.S. Congress passed the Gynecologic Cancer Education and Awareness Act of 2005 (known as Johanna's Law) to launch a campaign to "increase the awareness and knowledge of health care providers and women with respect to gynecologic cancers."

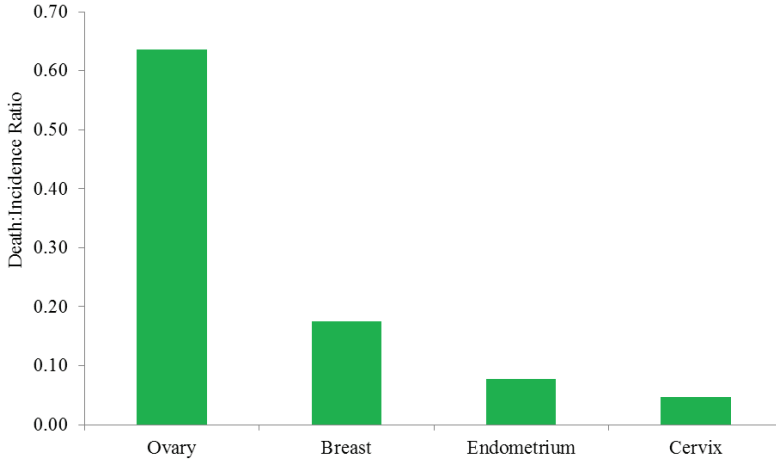

FIGURE S-1 The ratio between the death and incidence rates for ovarian, breast, endometrial, and cervical cancers per 100,000 women in the United States, 2008–2012.

Study Charge

In the fall of 2014, with support from the Centers for Disease Control and Prevention (CDC), the Institute of Medicine (IOM) formed the Committee on the State of the Science in Ovarian Cancer Research to examine and summarize the state of the science in ovarian cancer research, to identify key gaps in the evidence base and challenges to addressing those gaps, to consider opportunities for advancing ovarian cancer research, and to examine ways to disseminate new information to all stakeholders.

To guide its deliberative process, the committee developed a conceptual model to identify research gaps across the continuum of ovarian cancer care and also in critical areas of cross-cutting research (see Figure S-2).

Defining Ovarian Cancer

"Ovarian cancer" is a generic term often used for any primary malignant ovarian tumor, but it is a misnomer in the sense that ovarian cancer is not just one disease. Rather, it refers to a constellation of distinct types of cancer involving the ovary. Ovarian cancers with epithelial differentiation (carcinomas) represent the majority of malignant tumors and are responsible for most ovarian cancer–related deaths. This classification is complicated by recent evidence suggesting that many ovarian carcinomas do not arise in the ovary per se. Instead they may, in fact, arise in other tissues (e.g.,

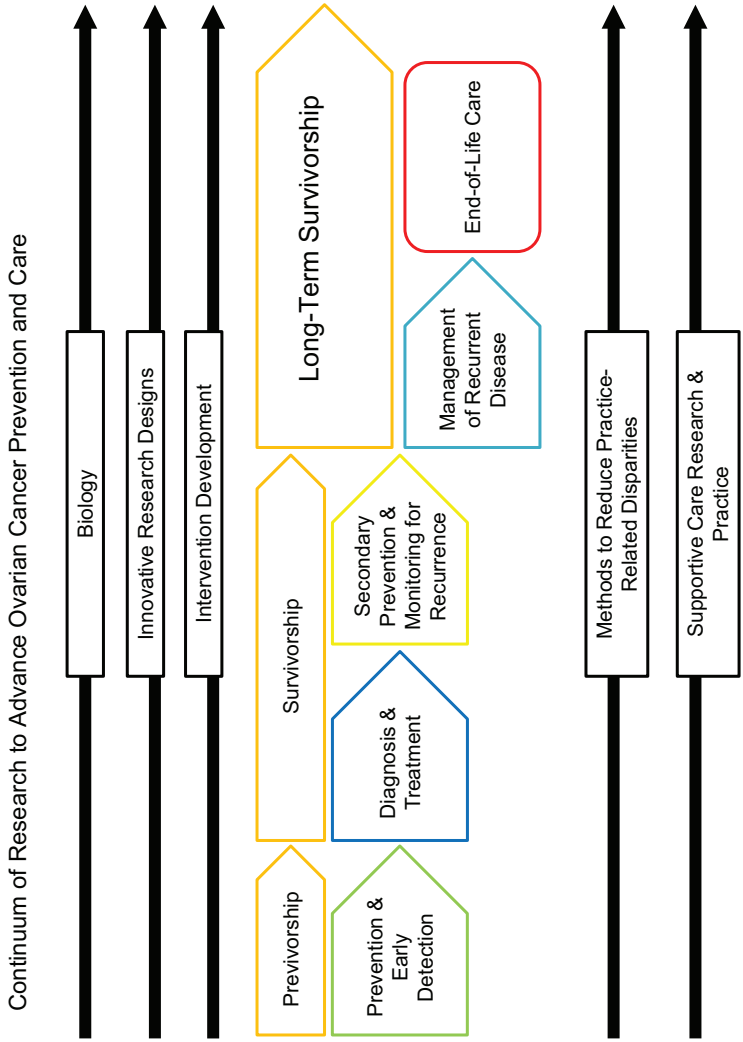

FIGURE S-2 Framework for research in ovarian cancer.
NOTE: Colored figures represent phases of the ovarian cancer care continuum where research can be focused. Black boxes indicate critical areas of ongoing cross-cutting research that span these phases.

the fallopian tubes) and then metastasize to the ovary, or arise from cells that are not considered intrinsic to the ovary (see Figure S-3).

Ovarian carcinomas themselves also represent a heterogeneous collection of different tumor types (see Figure S-4). Ovarian carcinomas account for more than 85 percent of ovarian cancers, and more than 70 percent of ovarian carcinomas are high-grade serous carcinomas (HGSCs). Consequently, this report focuses on ovarian carcinomas, with a particular emphasis on HGSCs, recognizing that other less common types of ovarian malignancies exist and are responsible for a smaller fraction of deaths.

RECOMMENDATIONS

The committee focused on identifying the research gaps that, if addressed, could have the greatest impact on reducing ovarian cancer morbidity or mortality. A wide variety of stakeholders are integral to ovarian cancer research, including the U.S. Congress, federal agencies (e.g., CDC, U.S. Department of Defense, U.S. Food and Drug Administration, National Institutes of Health), private foundations, industry, academic institutions, professional societies, and advocacy groups. Most of these stakeholders are engaged in research across the care continuum, and many are both funders and performers of research. The committee therefore concluded that directing research toward the gaps identified in the recommendations is the responsibility of all stakeholders in their individual and collaborative efforts to fund, perform, or advocate for ovarian cancer research.

The committee identified four overarching concepts that should be applied to each recommendation in this report:

- As the most common and lethal subtype, the study of HGSC needs to be given priority;
- Even so, more subtype-specific research is also needed to further define the differences among the various subtypes;
- Given the relative rarity and heterogeneity of ovarian cancers, collaborative research (including the pooling and sharing of data and biospecimen resources, such as through consortia) is essential; and
- The dissemination of new knowledge and the implementation of evidence-based interventions and practices are the final steps in the knowledge translation process.

These recommendations are intertwined and so need to be considered simultaneously, not sequentially. Their sequence should not be considered as indicating priority of importance or an order of implementation.

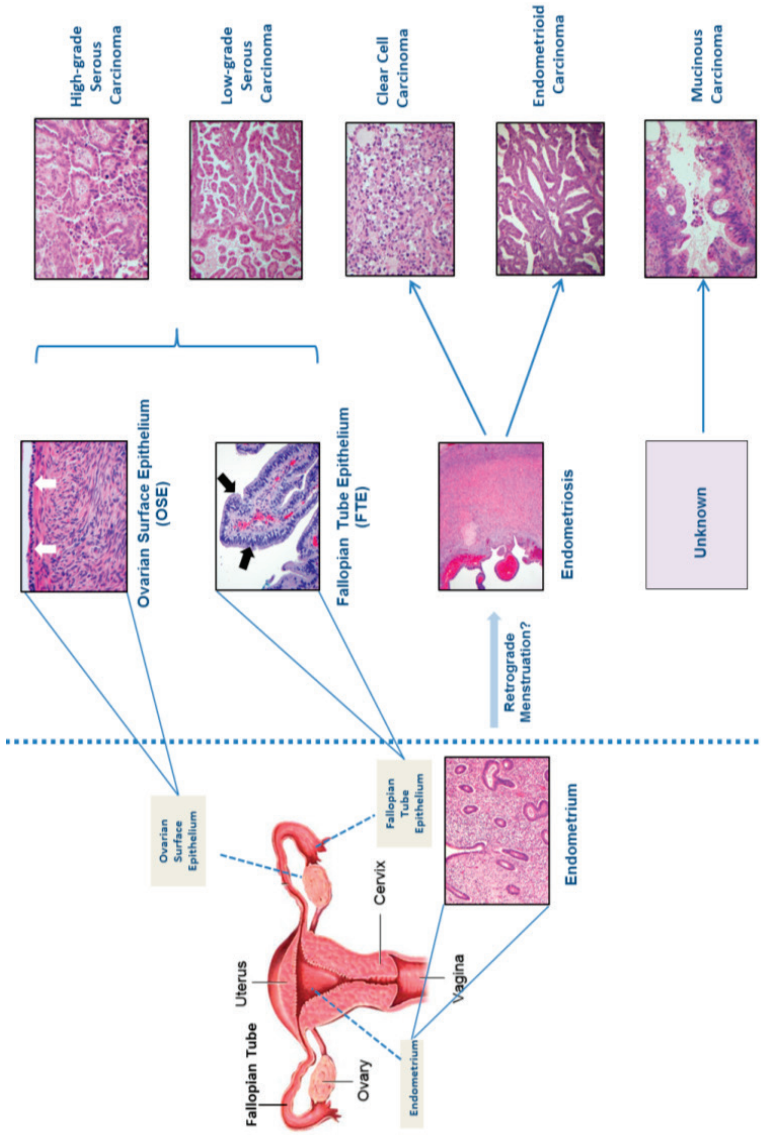

FIGURE S-3 Potential cellular origins of ovarian carcinomas.
NOTE: White arrows indicate ovarian surface epithelium (OSE); black arrows indicate fallopian tube epithelium (FTE).
SOURCE: Photographs of pathology slides reprinted with permission from Kathleen Cho (2016).

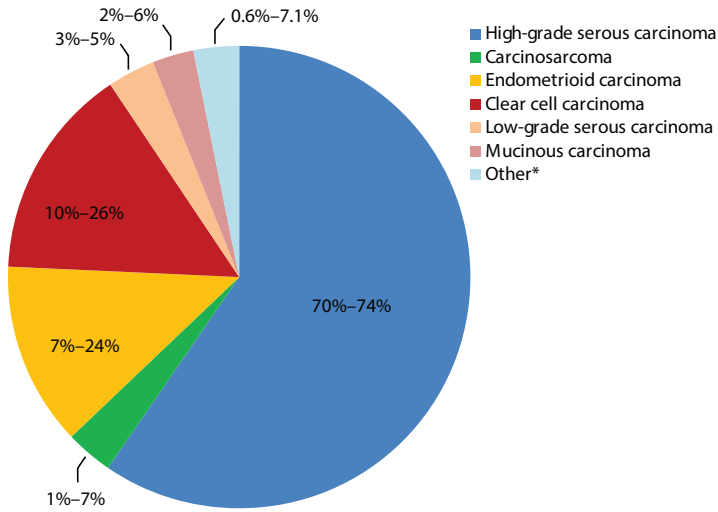

FIGURE S-4 Percentage of cases by major ovarian carcinoma subtype.
NOTE: Other* refers to mixed or transitional carcinomas where it is not possible to categorize to a single subtype.
SOURCES: Gilks et al., 2008; Seidman et al., 2003, 2004.

The Biology of Ovarian Cancer

Recent evidence suggests that many ovarian carcinomas do not arise in the ovary. Furthermore, researchers do not have a complete understanding for each subtype of how the disease progresses or the effects of the microenvironment. Without better model systems that replicate the manifestations of the human disease, the answers to many key questions will remain elusive. This research gap is further complicated by the significant degree of heterogeneity of ovarian carcinomas, including within and between subtypes. However, clinicians and researchers tend to combine them in many types of research. In spite of recent advances, the incomplete understanding of the basic biology of each subtype, including origin and pathogenesis, is an impediment to advances in prevention, screening and early detection, diagnosis, treatment, and supportive care.

RECOMMENDATION 1: Researchers and funding organizations should design and prioritize preclinical, clinical, and population-based research agendas that take into account the different ovarian cancer subtypes. A top priority should be elucidating the cellular origins and pathogenesis of each subtype. Particular attention should be paid to:

- **Tumor characteristics such as microenvironment, intratumoral heterogeneity, and progression pathways;**
- **The development of experimental model systems that reflect ovarian cancer heterogeneity; and**
- **Incorporation of the multi-subtype paradigm into prevention, screening, diagnosis, and treatment research.**

While it will be critical to apply this multi-subtype approach to research on ovarian cancer, an incomplete understanding of the biology of these cancers has prevented the emergence of uniform standards for describing the characteristics of the subtypes. Tumor classification, nomenclature, and grading systems have changed over time as new insights have emerged, and evidence suggests that there is substantial variability in current surgical and pathological practices for the reporting of ovarian cancers. The implementation of a single, uniformly implemented nomenclature and classification scheme (with standardized diagnostic criteria) is essential and will serve as the necessary foundation for all future research in ovarian cancer.

RECOMMENDATION 2: Pathology organizations, oncology professional groups, and ovarian cancer researchers should reach consensus on diagnostic criteria, nomenclature, and classification schemes that reflect the morphological and molecular heterogeneity of ovarian cancers, and they should promote the universal adoption of a standardized taxonomy.

Achieving this consensus will be complex. Multiple stakeholders will need to be engaged in an iterative process in which the schemes can change. Stakeholders can employ a variety of options for moving toward consensus, including the creation of ongoing working groups by subtype, as has been done in other diseases.

The committee again emphasizes that these recommendations about biology research and taxonomy need to be considered simultaneously. That is, a common taxonomy is needed based on the best currently available research, and research designs going forward will need to be based on this common taxonomy, but the taxonomy will also need to evolve as more is learned about the biology of the subtypes. For example, an improved understanding of molecular characterizations (see Recommendation 8) may, in fact, be more informative for classification than shared appearance. Simultaneously, an enhanced understanding of the characterizations of the subtypes will inform the development of targeted therapeutics (see Recommendation 9), and the drive for targeted therapeutics will, in turn, require more basic research on the biology of the ovarian cancer subtypes.

Risk Assessment, Screening, and Early Detection

Better methods for identifying high-risk women could facilitate the prevention or early detection of ovarian cancers. A family history of ovarian cancer, specific germline (inherited) genetic mutations, and certain hereditary cancer syndromes have strong associations with risk for ovarian cancer. The *BRCA1* and *BRCA2* genes are the most recognizable ovarian cancer risk-related genes, followed by the mismatch repair genes associated with Lynch syndrome. Several other risk-related genes have been identified but are less well studied. Although family history is linked to an increased risk for all ovarian cancer subtypes, it is most strongly linked with risk for HGSC, where up to 25 percent of women have a germline mutation. Multiple groups recommend that all women diagnosed with an invasive ovarian cancer receive genetic testing and counseling, for a variety of reasons, including to determine the appropriate therapies, to assess other health risks, and to estimate the risk for family members. Genetic counseling and testing are also recommended for the first-degree relatives of women with a hereditary cancer syndrome or germline mutation (i.e., cascade testing). For the first-degree relatives of women with ovarian cancer who have not had genetic testing, genetic counseling would be appropriate for assessing risk and the need for testing. Women without ovarian cancer who carry germline mutations associated with greatly increased risk for developing ovarian cancer (sometimes referred to as "previvors") may benefit from enhanced screening, risk-reducing procedures, or chemoprevention. However, referrals for genetic counseling and testing are hindered by various patient-, provider-, and system-level barriers, such as a patient's lack of awareness of her family history, the limited time that providers generally have to collect a family history, and complex and inconsistent referral criteria. Furthermore, more research is needed to determine the significance of known mutations and to discover new significant mutations for all subtypes.

RECOMMENDATION 3: Researchers, public health practitioners, and clinicians should develop and implement innovative strategies to increase genetic counseling and testing, as well as cascade testing for known germline genetic predispositions in appropriate populations (e.g., untested ovarian cancer survivors and relatives of individuals who tested positive). Furthermore, researchers, clinicians, and commercial laboratories should determine the analytic performance and clinical utility of testing for other germline mutations beyond *BRCA1* and *BRCA2* and the mismatch repair genes associated with Lynch syndrome.

Risk cannot be fully assessed by relying on family history alone. Up to one-half of women with high-risk germline mutations do not have an ap-

parent family history of breast or ovarian cancer, and family history may not identify risk for women with few female relatives or for women who do not know the family health history of one or both parents. Furthermore, as the majority of women with ovarian cancer do not appear to have a known high-risk germline mutation or a significant family history, it is critical to consider other potential risk factors. While several nongenetic factors are associated with either an increased or a decreased risk for developing ovarian cancer, the patterns of association are inconsistent, and the strongest factors to date are those associated with the less common and less lethal subtypes.

RECOMMENDATION 4: Researchers and funding organizations should identify and evaluate the underlying mechanisms of both new and established risk factors for ovarian cancers in order to develop and validate a dynamic risk assessment tool accounting for the various ovarian cancer subtypes. Furthermore, a spectrum of risk factors should be considered, including genetics, hormonal and other biological markers, behavioral and social factors, and environmental exposures.

Collaborations between clinicians and population and basic scientists will help identify potential new risk factors and also provide an opportunity to better understand how specific exposures influence disease development. Current research does not provide insight as into which risk factors need to be prioritized for future research. In light of the heterogeneity of the cell of origin, an emphasis on factors that influence early carcinogenesis may have the largest impact on identifying women at high risk.

Women known to be at high risk may benefit from nonsurgical and surgical preventive measures, but the risk–benefit ratios of these measures need to be better defined for different subtypes and at-risk populations. For example, the use of prescription medications (e.g., oral contraceptives) and risk-reducing surgeries (e.g., bilateral salpingo-oophorectomy and salpingectomy) need to be weighed against potential complications and long-term side effects (e.g., stroke risk, risk for other cancers, surgical complications, and overall mortality). As new prevention strategies are developed, researchers will need to amass an evidence base for their efficacy as well as their potential long-term harm.

RECOMMENDATION 5: Clinicians, researchers, and funding organizations should focus on quantifying the risk–benefit balance of nonsurgical and surgical prevention strategies for specific subtypes and at-risk populations.

Current approaches for early detection include assaying for biomarkers, often in combination with imaging technologies. While the use of these strategies in large screening trials has resulted in more ovarian cancers being detected at earlier stages, to date they have not had a substantial impact on overall mortality. Given the marked heterogeneity of ovarian cancers and the incomplete understanding of early disease development for each subtype, it is highly unlikely that a single biomarker or imaging modality will be sufficient to aid in the early detection of all the subtypes. While research on refining current methods may be fruitful, distinct multimodal approaches will likely be needed to detect each of the various subtypes at their earliest stages.

RECOMMENDATION 6: Researchers and funding organizations should focus on the development and assessment of early detection strategies that extend beyond current imaging modalities and biomarkers and that reflect the pathobiology of each ovarian cancer subtype.

Going forward, screening trials may be more informative if conducted in populations with elevated ovarian cancer risk. Research on the impact of earlier detection on quality of life will also be important.

Diagnosis and Treatment

Compared to the situation over the past few decades, newly diagnosed ovarian cancers are now being more accurately and consistently staged, and a wider variety of treatment options exist. Most women with newly diagnosed ovarian cancer undergo primary debulking surgery (PDS) to remove as much of the grossly visible tumor as possible (cytoreduction), as well as to make it possible to determine a specific diagnosis (e.g., subtype, staging). Survival is markedly better for women who have complete (or optimal) tumor resection, yet great variability exists in the extent of tumor resection. For women in whom an optimal resection is not thought to be feasible, or who are unable to undergo PDS due to comorbidities, neoadjuvant chemotherapy (NACT) can reduce tumor size and facilitate subsequent resection. After surgery, women typically receive multiple cycles of chemotherapy. While the majority of women respond well to initial treatment, most will experience a recurrence of the disease, resulting in a cycle of repeated surgeries and additional rounds of chemotherapy.

Standard of Care

Several organizations have developed national clinical practice guidelines for the assessment and treatment of women with both newly diag-

nosed and recurrent ovarian cancers. While women who receive care in accordance with these guidelines have considerably better clinical outcomes (e.g., improved survival and fewer surgical complications), less than one-half of women with ovarian cancer receive such care. For example, while the intraperitoneal (IP) route for the delivery of chemotherapy offers notable advantages over intravenous (IV) and oral routes, the adoption of IP chemotherapy protocols is not widespread. However, this is due in part to concerns regarding the efficacy and potential adverse effects of IP administration, and the better side-effects profile associated with newer IV regimens. In addition to the variation in adherence to standards of care for surgery and chemotherapy, the guidelines for cancer genetics referrals are not routinely or widely implemented (see Recommendation 3). Testing for germline mutations among women newly diagnosed with ovarian cancer is important because the presence of certain mutations informs therapy decisions.

Being treated by a gynecologic oncologist and having treatment in a high-volume hospital or cancer center are the two most significant predictors of whether a woman with ovarian cancer will receive the standard of care, and both are associated with better outcomes, but access to such care can be a challenge. Significant predictors of nonadherence to the standard of care include the patient being of advanced age at diagnosis, the presence of treatment-limiting comorbidities, being of a nonwhite race, and having a lower socioeconomic status. Like most other cancers, ovarian cancer primarily affects older adults, but little is known about the care of older women with ovarian cancer. For example, older women with comorbidities may be precluded from receiving the standard of care, which, in turn, may lead to worse outcomes. Also, historical trends show differences in outcomes by race, but the reasons for this are unknown. Finally, more research is needed on how quality metrics (including measures of outcomes) can help drive continuous quality improvement in ovarian cancer care. The current patterns of care reveal inconsistencies in therapeutic approaches and disparities in care delivery, which may contribute to poorer outcomes.

RECOMMENDATION 7: To reduce disparities in health care delivery and outcomes, clinicians and researchers should investigate methods to ensure the consistent implementation of current standards of care (e.g., access to specialist care, surgical management, chemotherapy regimen and route of administration, and universal germline genetic testing for newly diagnosed women) that are linked to quality metrics.

However, no one model of care will serve all patients in all settings. For example, women in rural settings may not have access to a gynecologic oncologist or a high-volume cancer center. Therefore, it will be necessary

to explore innovative models of care that can help deliver the standard of care, such as the use of telemedicine for consultation and the use of patient navigation systems to support self-management. The committee recognizes that, as is the case in other areas of health care, issues such as payment, policy, and education and training of the health care workforce affect the delivery of the standard of care, and so these issues will also need further examination as new models are developed.

Predicting Response

While adherence to standards of care leads to improved outcomes, little is known about why some women respond better to specific surgical and chemotherapeutic therapies, or about how age affects treatment. For example, the question of which women should receive initial PDS or NACT remains unresolved. It may be that women with certain subtypes respond better to different therapies or that women who respond particularly well to a given treatment may share characteristics that extend beyond their tumor subtype.

Current classification systems also do not, for the most part, help to tailor treatment regimens. Recurrent ovarian cancers have traditionally been categorized as platinum sensitive if recurrence is diagnosed more than 6 months from prior therapy or platinum resistant if recurrence is diagnosed less than 6 months from prior therapy, but this classification does not reflect the mechanisms of recurrent disease. Several assays have been developed (or are in development) to determine the likelihood of primary and recurrent tumors' ability to respond to various chemotherapeutic agents, but at this time none of them have been validated.

RECOMMENDATION 8: Clinicians and researchers should focus on improving current treatment strategies, including

- **a. The development and validation of comprehensive clinical, histopathologic, and molecular characterizations that better inform precision medicine approaches for women with newly diagnosed and recurrent disease;**
- **b. Advancement in the understanding of the mechanisms of recurrent and drug-resistant (e.g., platinum-resistant) disease and the development of a more informative classification system;**
- **c. The identification of predictors of response to therapy and near-term indicators of efficacy; and**
- **d. The determination of the optimal type and timing of surgery in women newly diagnosed with ovarian cancer and of the efficacy of subsequent cytoreduction procedures for women with recurrent disease.**

Several modalities can be used to match individual patients to specific procedures and treatments. The analysis of biomarkers, the determination of the molecular features of tumors, minimally invasive assessments (e.g., laparoscopy), and the use of imaging all provide insights. Similarly, a variety of approaches can be used to predict therapeutic efficacy, including scoring systems, genetic panel testing, and molecular profiling. The knowledge gained through these precision medicine approaches will also help to inform the development of new and better treatments.

Developing Better Treatments

While clinicians need better ways to select the most appropriate among existing treatments for individual patients, they also need more treatment options, and the development of better treatments depends in large part on the clinical trials system. The 2010 IOM report *A National Cancer Clinical Trials System for the 21st Century* outlined principles to improve the clinical trials system in general, including

- Improve collaboration among stakeholders, including the use of consortia;
- Define an effective mechanism for combining products in clinical trials;
- Develop and evaluate novel trial designs;
- Increase the accrual volume, diversity, and speed of clinical trials; and
- Educate patients about the availability, payment coverage, and value of clinical trials.

These principles are particularly relevant for ovarian cancer research, given the relative rarity of the disease combined with the diversity of subtypes. Comparative effectiveness studies, combination therapies, and multimodality strategies will all be important. This committee endorses these principles and suggests that they be applied to all recommendations related to clinical trials for ovarian cancer research.

Clinicians currently have few options for drug therapy, and the long-term efficacy of these agents is limited by a high rate of drug resistance. A better understanding of the diversity of ovarian cancers will offer the potential for targeted treatments. Innovative early phase clinical trial designs that incorporate biomarkers predictive of efficacy are needed to help identify which subtypes are likely to be responsive to specific new therapies. However, selecting clinically meaningful endpoints for trials in ovarian cancer can be challenging. For example, it may be difficult to determine the impact of a single agent on overall survival because women have typi-

cally had multiple previous therapies. Patient preferences also need to be considered in assessing the effectiveness of new therapies (e.g., the tolerable levels of side effects, given the expected outcomes). Furthermore, little research exists on nonpharmacologic therapies and interventions (e.g., diet, exercise, stress reduction) that might affect response to treatment. Overall, the current standard of care lacks precision medicine approaches to therapy.

RECOMMENDATION 9: Researchers should develop more effective pharmacologic and nonpharmacologic therapies and combinations of therapies that take into account the unique biology and clinical course of ovarian cancer. These approaches should include

- **a. Developing immunologic and molecularly driven treatment approaches specific to the different ovarian cancer subtypes;**
- **b. Identifying markers of therapeutic resistance and exceptional response; and**
- **c. Using interdisciplinary teams to design and conduct statistically efficient and information-rich clinical studies.**

The development of new approaches, however, will depend on developing a better understanding of the basic biology of the ovarian cancer subtypes (see Recommendation 1). As the committee did not find evidence for the superiority of any single treatment, it concluded that a variety of approaches need to be evaluated, including new combinations of existing drugs, new drug formulations, targeted biologics, protein inhibitors, *TP53*-directed therapies, anti-angiogenics, immunotherapies, and nonpharmacologic interventions. All of these approaches have merit because their effectiveness may vary within and among subtypes.

Supportive Care Along the Survivorship Trajectory

Most research on ovarian cancers focuses on the treatment of the disease rather than on how to improve the management of the acute and long-term physical and psychosocial effects of diagnosis and treatment across the trajectory of survivorship. Although research on therapies that may provide life-saving benefit is crucial, complementary research on how to best support women living with ovarian cancer and improve their quality of life is also important for them and their families. Women with ovarian cancer require early and ongoing supportive care to ensure that aggressive, life-extending treatments are enhanced by multidisciplinary supportive care to maximize quality of life.

The 2013 IOM report *Delivering High-Quality Cancer Care* stated, "A high-quality cancer care delivery system depends on clinical research that gathers evidence of the benefits and harms of various treatment options

so that patients, in consultation with their clinicians, can make treatment decisions that are consistent with their needs, values, and preferences." However, for women with ovarian cancer, shared decision making and the management of the physical and psychosocial effects of diagnosis and treatment may be neglected in the effort to urgently address the disease, which is typically at an advanced stage at diagnosis. Also, a lack of professional expertise or resources may hinder joint decision making.

Current research provides little insight as to which women are most likely to suffer physical and psychosocial effects due to their diagnosis and treatment, or the best approaches for managing these effects. Furthermore, there may be differences in the needs of and best approaches for women of different demographic groups (e.g., older women versus younger women and women of different racial and ethnic groups). These research gaps may be addressed by more effective assessment of patient-reported symptoms and outcomes during treatment, especially on the outcomes that are most important to women (e.g., improved quality of life versus overall survival). Approaches to enhancing self-management, including leveraging mobile health technologies, need to be explored. Finally, as many women with ovarian cancer continue active treatment until the end of their lives, researchers need to help better define when disease-focused treatments are unlikely to be effective and the focus needs to shift to end-of-life care.

A majority of women with ovarian cancer require long-term active disease management, necessitating more effective approaches for supportive care and self-management.

RECOMMENDATION 10: Researchers and funding organizations should study the supportive care needs of patients with ovarian cancer throughout the disease trajectory, including

- **a. Identifying the array of factors that put women at high risk for poor physical and psychosocial outcomes;**
- **b. Identifying and overcoming barriers to the systematic assessment of the physical and psychosocial effects of disease and treatment;**
- **c. Developing and implementing more effective supportive care and self-management interventions; and**
- **d. Defining the parameters that indicate when patients and their families would benefit from transitioning to end-of-life care.**

Many of the supportive care needs of women with ovarian cancer are similar to those of women with other cancers. The committee endorses the following principles from previous IOM reports:

- Develop clinical tools and strategies to ensure that all cancer patients receive the standard of psychosocial care, including

  - Approaches for improving patient–provider communication and providing decision support,
  - Screening instruments to identify psychosocial problems,
  - Needs assessment instruments for psychosocial care planning, and
  - Illness and wellness management interventions.
- Provide patients and their families with understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of costs.
- Develop a common set of data elements that capture patient-reported outcomes, relevant patient characteristics, and health behaviors.
- Provide fact-based information to encourage advance care planning.
- Provide end-of-life care consistent with individual needs, values, and preferences.

Dissemination and Implementation

Amassing evidence on risk factors, treatments, and preventive strategies is not sufficient to ensure that this knowledge will be acquired and used by all stakeholders. A number of factors influence the movement of science into regular and effective use, including the complexity of health care systems, the capacity of practitioners and providers to absorb new knowledge, and the diversity of stakeholders. While the knowledge base on ovarian cancers has advanced, not all stakeholder groups are receiving important messages. This may contribute to the current variability seen in the delivery of the standard of care which, in turn, affects patient outcomes.

RECOMMENDATION 11: Stakeholders in ovarian cancer research, clinical care, and advocacy should coordinate the efforts to develop and implement efficient, effective, and reliable methods for the rapid dissemination and implementation of evidence-based information and practices to patients, families, health care providers, advocates, and other relevant parties. These efforts should include

a. Researching impediments to adopting current evidence-based practices;
b. Using multiple existing dissemination modalities (e.g., continuing education, advocacy efforts) to distribute messages strongly supported by the evidence base; and
c. Evaluating newer pathways of dissemination and implementation (e.g., social media, telemedicine with specialists).

CONCLUSION

While progress has been made in understanding ovarian cancers over the past few decades, much remains to be learned, especially about the origins and mechanisms of development—fundamental knowledge that could change paradigms for prevention, screening and early detection, and treatment. Improved communication is also needed to recognize ovarian cancer as a constellation of many types of cancer involving the ovary. A focus on distinct areas of research within and across the continuum of ovarian cancer care will help improve the lives of all women at risk for or diagnosed with an ovarian cancer.

1

Introduction and Background

Although recent years have seen many promising advances in cancer research, there remain surprising gaps in the fundamental knowledge about and understanding of ovarian cancer. Researchers now know that ovarian cancer, like many other types of cancer, should not be thought of as a single disease; instead, several distinct subtypes exist with different origins, different risk factors, different genetic mutations, different biological behaviors, and different prognoses, and much remains to be learned about them. For example, researchers do not have definitive knowledge of exactly where these various ovarian cancers originate and how they develop. Such unanswered questions have impeded progress in the prevention, early detection, treatment, and management of ovarian cancers. In particular, the failure to achieve major reductions in ovarian cancer morbidity and mortality during the past several decades is likely due to several factors, including

- A lack of research focusing on specific disease subtypes;
- An incomplete understanding of genetic and nongenetic risk factors;
- An inability to develop and validate effective screening and early detection tools;
- Inconsistency in the delivery of the standard of care;
- Limited evidence-based personalized medicine approaches tailored to the disease subtypes and other tumor characteristics; and
- Limited attention paid to research on survivorship issues, including supportive care with long-term management of active disease.

The symptoms of ovarian cancers can be nonspecific and are often not seen as indicating a serious illness by women or their health care providers until the symptoms worsen, at which point the cancer may be widespread and difficult to cure. The fact that these cancers are not diagnosed in many women until they are at an advanced stage is a major factor contributing to the high mortality rate for ovarian cancer, especially for women with high-grade serous carcinoma (HGSC)—the most common and lethal subtype. Indeed, roughly two-thirds of women with ovarian cancer are diagnosed with an advanced-stage cancer or with a cancer that has not been definitively staged, and the 5-year survival rate for these women is less than 30 percent (Howlader et al., 2015). Although many ovarian cancers respond well to initial treatment, including the surgical removal of grossly visible tumor (cytoreduction) and chemotherapy, the vast majority of the tumors recur. Recurrent ovarian cancers may again respond to further treatment, but virtually all of them will ultimately become resistant to current drug therapies.

Finally, less emphasis has been placed on research that focuses on how to improve therapeutic interventions by subtype or on how to reduce the morbidity of ovarian cancers. Little emphasis has been placed on understanding survivorship issues and the supportive care needs of women with ovarian cancer, including management of the physical side effects of treatment (including both initial and chronic, ongoing therapies) and addressing the psychosocial effects of diagnosis and treatment. The lasting impact of a diagnosis of ovarian cancer and its related treatment can be significant both for the women who experience recurrent disease and for the women who experience long (or indefinite) periods of remission. This report gives an overview of the state of the science in ovarian cancer research, highlights the major gaps in knowledge in that field, and provides recommendations that might help reduce the incidence of and morbidity and mortality from ovarian cancers by focusing on promising research themes and technologies that could advance risk prediction, early detection, comprehensive care, and cure.

STUDY CHARGE AND APPROACH

In spite of their high mortality rates, ovarian cancers often do not receive as much attention as other cancers. In part, this is because ovarian cancers are relatively uncommon. Furthermore, ovarian cancer has been called a "silent killer" because researchers once believed that there were no perceptible symptoms in the earlier stages of the disease (Goff, 2012). However, more recent research has shown that most women diagnosed with ovarian cancer report symptoms such as bloating, pelvic or abdominal pain, and urinary symptoms, and many women recall having these symptoms

for an extended period of time before diagnosis (Goff et al., 2000, 2004). Often, due to the nonspecific nature of ovarian cancer symptoms, patients and physicians do not recognize these early symptoms as indicative of ovarian cancer (Gajjar et al., 2012; Jones et al., 2010; Lockwood-Rayermann et al., 2009).

In this context, in 2006 the U.S. Congress passed the Gynecologic Cancer Education and Awareness Act of 2005,[1] which amended the Public Health Service Act (42 U.S.C. 247b-17) to direct the secretary of the U.S. Department of Health and Human Services to launch a campaign to "increase the awareness and knowledge of health care providers and women with respect to gynecologic cancers." The law is commonly known as Johanna's Law in memory of Johanna Silver Gordon, a public school teacher from Michigan who died from late-stage ovarian cancer (Twombly, 2007). The law was reauthorized in 2010,[2] and, as part of the Consolidated Appropriations Act of 2014, Congress directed the Centers for Disease Control and Prevention (CDC) to use funds from Johanna's Law to perform a review of the state of the science in ovarian cancer.[3]

Study Charge

In the fall of 2014, with support from the CDC, the Institute of Medicine (IOM) formed the Committee on the State of the Science in Ovarian Cancer Research to examine and summarize the state of the science in ovarian cancer research, to identify key gaps in the evidence base and challenges to addressing those gaps, and to consider opportunities for advancing ovarian cancer research (see Box 1-1). The committee determined that the best way to facilitate progress in reducing morbidity and mortality would be to identify the research gaps that were most salient and that, if addressed, could affect the greatest number of women.

The committee was also asked to consider ways to translate and disseminate new findings and to communicate these findings to all stakeholders. This report, therefore, not only describes evidence-based approaches to translation and dissemination, but it also suggests strategies for communicating those approaches.

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[1] Gynecologic Cancer Education and Awareness Act of 2005, Public Law 475, 109th Cong., 2nd sess. (January 12, 2007).

[2] To reauthorize and enhance Johanna's Law to increase public awareness and knowledge with respect to gynecologic cancers, Public Law 324, 111th Cong., 2nd sess. (December 22, 2010).

[3] *Explanatory statement submitted by Mr. Rogers of Kentucky, Chairman of the House Committee on Appropriations regarding the House amendment to the Senate amendment on H.R. 3547, consolidated…*, 113th Cong., 2nd sess., Congressional Record 160, no. 9, daily ed. (January 15, 2014):H 1035.

BOX 1-1
Statement of Task

An ad hoc committee under the auspices of the Institute of Medicine will review the state of the science in ovarian cancer research and formulate recommendations for action to advance the field. The committee will:

- Summarize and examine the state of the science in ovarian cancer research;
- Identify key gaps in the evidence base and the challenges to addressing those gaps;
- Consider opportunities for advancing ovarian cancer research; and
- Examine avenues for translation and dissemination of new findings and communication of new information to patients and others.

The committee will make recommendations for public- and private-sector efforts that could facilitate progress in reducing the incidence of and morbidity and mortality from ovarian cancer.

The committee emphasizes that its charge was to focus on research in ovarian cancer and, particularly, to focus on the gaps in the evidence base that, if addressed, would have the greatest impact on the lives of women diagnosed with or at risk for ovarian cancer. The committee did not explore issues affecting the care of women with ovarian cancer (e.g., health insurance coverage and policy issues) in depth. For example, while the regulatory process for drug approval is interconnected with the clinical trial enterprise (e.g., the design of clinical trials may determine what data are gathered and, in turn, affect the approval process), a full examination of issues related to the approval of new drugs was beyond the scope of this report. Furthermore, it was outside the scope of this report to fully evaluate specific research programs in ovarian cancer. In addition, this report does not offer an exhaustive cataloguing of every actor engaged in ovarian cancer research, nor does it detail every effort made by stakeholders to engage in dissemination and implementation efforts. Rather, the examples given in this report are meant to highlight the efforts being made, recognizing there are many other similar efforts.

Finally, the committee focused as much as possible on the research gaps and the challenges to addressing those gaps that are unique to ovarian cancer. However, those research gaps and challenges that are common to all types of cancer research, or even to all health care research, are described as appropriate. For example, while the clinical trials system is extremely important to the ovarian cancer research enterprise, many of the outstanding

questions and concerns related to the clinical trials system are shared with all types of cancer research and could not be explored or discussed in detail. Therefore, the committee turned to previous IOM reports specific to the clinical trials system in general for guidance, and then considered aspects of the system that are particularly relevant for ovarian cancer research.

Study Approach

The study committee included 15 members with expertise in ovarian cancer, gynecologic oncology, gynecologic pathology, gynecologic surgery, molecular biology, cancer genetics and genomics, genetic counseling, cancer epidemiology, immunology, biostatistics, bioethics, advocacy, survivorship, and health communication. (See Appendix E for biographies of the committee members.)

A variety of sources informed the committee's work. The committee met in person four times, and during two of those meetings it held public sessions to obtain input from a broad range of relevant stakeholders. In addition, the committee conducted extensive literature reviews, reached out to a variety of public and private stakeholders, and commissioned one paper.

The committee encountered a number of challenges. In some cases, it found itself limited by what was available in the published literature. At other times, it was challenged by the use of different methodologies for the classification of ovarian cancers in the research literature. For instance, many studies in the literature consolidate all types of ovarian cancer instead of studying and reporting them by subtype. In its review of the evidence, the committee discerns, where possible, whether the reported findings apply to ovarian cancers as a whole or to particular subtypes. One other major challenge to reviewing and summarizing the evidence base on ovarian cancer, particularly in summarizing the epidemiology by subtype, was the way that the grading, classification, and nomenclature for ovarian cancers have varied over the years.

In order to guide its deliberative process, the committee chose to make recommendations about research gaps based on the continuum of cancer care (see Figure 1-1). The committee focused on cross-cutting research areas critical to each phase of the continuum: the basic biology of ovarian cancers, innovative clinical trial design, intervention development, methods to reduce practice-related disparities, and supportive care research and practice. Finally, the committee considered evidence and strategies for the dissemination and implementation of knowledge across all of these domains.

DEFINITIONS OF KEY TERMS

This section provides definitions of several key terms that are relevant to this report, and also provides an explanation of how the committee

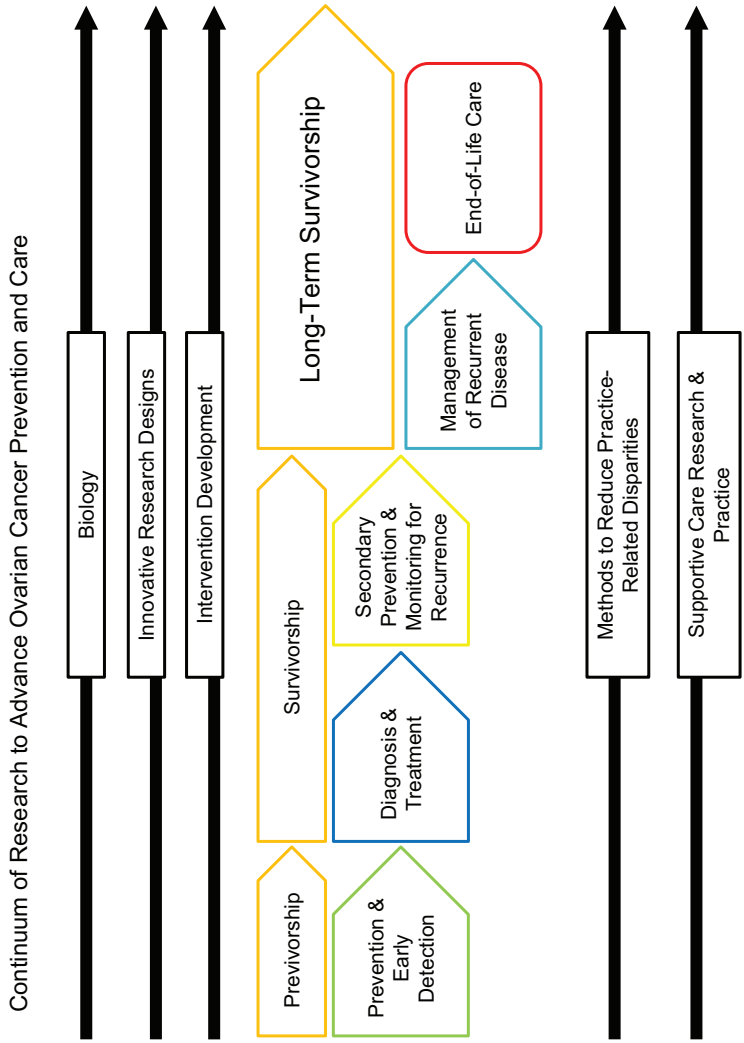

FIGURE 1-1 Framework for research in ovarian cancer.
NOTE: Colored figures represent phases of the ovarian cancer care continuum where research can be focused. Black boxes indicate critical areas of ongoing cross-cutting research that span these phases.

selected terms for consistency throughout the report. A glossary including more terms is provided in Appendix B, and a list of key acronyms is included in Appendix A.

Target Population

This report is concerned with women with ovarian cancers. However, the committee recognizes that there is a small subpopulation of transgender men who may be at risk for ovarian cancers, particularly due to the use of testosterone therapy (Dizon et al., 2006; Hage et al., 2000).

Basic Cancer Terminology

The terms "cancer," "carcinoma," and "tumor" can be confused or interchanged at times. *Cancer* is "a term for diseases in which abnormal cells divide without control and can invade nearby tissues," while a *tumor* (which can be cancerous or noncancerous) is "an abnormal mass of tissue that results when cells divide more than they should or do not die when they should" (NCI, 2015d). *Carcinomas* are cancers that "begin in the skin or in tissues that line or cover internal organs" (i.e., arising from epithelial cells) (NCI, 2015d). As was noted previously, this report focuses on ovarian carcinomas, because they are the most common and most lethal of the ovarian cancer subtypes.

While the committee endeavored to focus on carcinomas wherever possible, there were times when that was not possible, and the terms "cancer" and "tumor" are used when appropriate. For example, many studies are based on ovarian cancers collectively and do not analyze data based on the subtypes. The committee also uses the term "tumor" when discussing the physical mass itself. Finally, although the term "ovarian cancer" technically represents an array of disease subtypes, the committee refers to the disease in the plural form (i.e., "ovarian cancers") whenever appropriate in order to emphasize the heterogeneity of the disease and all its subtypes.

When ovarian cancer reappears in a woman, it is usually referred to as "relapsed" or "recurrent" disease. The National Cancer Institute (NCI) defines *cancer recurrence* as "cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body" (NCI, 2015d). Noting that a cancer that has recurred is also called "relapsed cancer," the NCI defines *relapse* as "the return of a disease or the signs and symptoms of a disease after a period of improvement." In this report, for consistency the committee uses only the terms "recurrent" or "recurrence"—and not "relapsed" or "relapse"—but

it recognizes that there may be subtle differences, preferences, or interpretations in the use of the two terms.

DEFINING AND CLASSIFYING OVARIAN CANCERS

"Ovarian cancer" is a generic term that can be used for any cancer involving the ovaries. The ovaries are composed of several different cell types, including the germ cells, specialized gonadal stromal cells (e.g., granulosa cells, theca cells, Leydig cells, and fibroblasts), and epithelial cells; ovarian cancers can arise from any of these cell types. Ovarian cancers with epithelial differentiation (carcinomas) account for more than 85 percent of ovarian cancers and are responsible for most ovarian cancer–related deaths (Berek and Bast, 2003; Braicu et al., 2011; SEER Program, 2015; Seidman et al., 2004). Consequently, this report will focus on the biology of ovarian carcinomas, while recognizing that although other, less common types of ovarian malignancies do exist, they are responsible for a smaller fraction of ovarian cancer–related deaths.

As with ovarian cancers in general, ovarian carcinomas are quite heterogeneous and come in a variety of different tumor types (see Figure 1-2). The major ovarian carcinoma subtypes are named according to how closely the tumor cells resemble normal cells lining different organs in the female genitourinary tract. Specifically, serous, endometrioid, and a subset

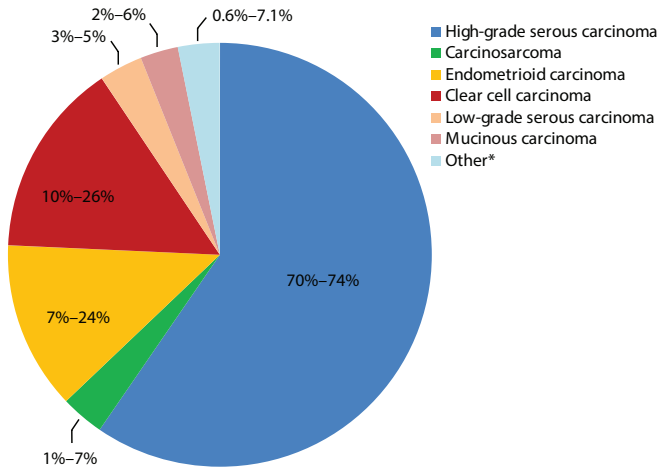

FIGURE 1-2 Percentage of cases by major ovarian carcinoma subtype.
NOTE: Other* refers to mixed or transitional carcinomas where it is not possible to categorize to a single subtype.
SOURCES: Gilks et al., 2008; Seidman et al., 2003, 2004.

of mucinous carcinomas exhibit morphological features that are similar to normal epithelial cells in the fallopian tube, endometrium, and endocervix, respectively. Furthermore, clear cell carcinomas resemble cells seen in the gestational endometrium (Scully et al., 1999).

Over the past several years, researchers have developed a streamlined classification scheme in which the majority of ovarian carcinomas can be divided into five types:

1. HGSC,
2. Endometrioid carcinoma (EC),
3. Clear cell carcinoma (CCC),
4. Low-grade serous carcinoma (LGSC), and
5. Mucinous carcinoma (MC) (Gurung et al., 2013; Kalloger et al., 2011).

Some researchers have offered an even simpler classification with a scheme in which ovarian carcinomas are divided into Type I and Type II tumors based on shared features (Shih and Kurman, 2004). In this scheme, Type I carcinomas are low-grade, relatively unaggressive, and genetically stable tumors that often arise from recognizable precursor lesions such as endometriosis or benign tumors and frequently harbor somatic mutations that deregulate specific cell signaling pathways or chromatin remodeling complexes. ECs, CCCs, MCs, and LGSCs are considered Type I tumors and are often characterized by *KRAS*, *BRAF*, or *PTEN* mutations. Type II carcinomas are high-grade, biologically aggressive tumors from their inception, with a propensity for metastasis from small, even microscopic, primary lesions. HGSCs represent the majority of Type II tumors and are characterized by the mutation of *TP53* and frequent mutations of genes (e.g., *BRCA1* and *BRCA2*) that lead to homologous recombination defects (Pennington et al., 2014).

Because the data collected thus far provide compelling evidence that each of the various Type I tumors has distinct biological and molecular features, these tumors will be referred to by their specific histologic type throughout the remainder of this report. However, the Type I and Type II terminology will be used where necessary, most often in referring to studies conducted using this classification scheme. Furthermore, because the majority of ovarian carcinomas are HGSCs, and HGSCs are the subtype with the worst prognosis, this report will primarily focus on this subtype. When referring to historical or large-scale epidemiologic studies of ovarian cancer for which the tumor subtypes were not specified, readers can reasonably assume that most of the tumors were HGSCs.

After being classified by subtype, tumors are usually also assigned a grade, based on how closely the tumor cells resemble their normal counter-

parts. Both two-grade and three-grade systems have been applied in various situations; in both types of systems, the lower-grade tumors more closely resemble normal cells than the higher-grade tumors (Malpica et al., 2004; Silverberg, 2000).

OVARIAN CANCER PATTERNS AND DEMOGRAPHICS[4]

Although ovarian cancer is relatively rare, it is one of the deadliest cancers. It was estimated that more than 21,000 women in the United States would receive a diagnosis of an ovarian cancer in the year 2015[5] (Howlader et al., 2015). This represents almost 12 new cases for every 100,000 women and 2.6 percent of all new cancer cases in women in the United States. Nearly 200,000 women in the United States are living with ovarian cancer in any given year, and approximately 1.3 percent of all American women will be diagnosed with ovarian cancer at some point in their lives, which qualifies ovarian cancer as a rare disease as defined by the National Institutes of Health (NIH) Genetic and Rare Diseases Information Center (NIH, 2015a). Still, according to estimates, more than 14,000 American women will have died from ovarian cancer in 2015, which corresponds to approximately 7.7 deaths per 100,000 women and 5.1 percent of all cancer deaths among American women (ACS, 2015; Howlader et al., 2015). Despite its relatively low incidence, ovarian cancer is the fifth leading cause of cancer deaths among U.S. women and the eighth leading cause of women's cancer deaths worldwide (Ferlay et al., 2015; Howlader et al., 2015). By comparison, breast cancer is more common—among American women the estimated number of new cases of breast cancer each year is 10 times the number of new cases of ovarian cancer—but ovarian cancer is more deadly, with a death-to-incidence ratio that is more than three times higher than for breast cancer (Howlader et al., 2015) (see Figure 1-3).

The survival rate for ovarian cancer is quite low. For 2005 to 2011, the 5-year survival rate in the United States was just 45.6 percent. By contrast, the 5-year survival rate in the United States for the same period was nearly 90 percent for breast cancer, more than 80 percent for endometrial cancer, and nearly 70 percent for cervical cancer. However, given the typical course of initial remission and subsequent recurrence for women with ovarian cancer, the 5-year survival metric may not reflect the overall disease course. At advanced stages, MCs and CCCs in particular have poorer prognoses and survival rates than other carcinoma subtypes (Mackay et al., 2010).

[4]Terminology to describe race and ethnicity reflects the terminology used in the original sources.

[5]Because historical epidemiologic data typically combine the multiple types of ovarian cancer, they are discussed as a single disease in this discussion of epidemiology.

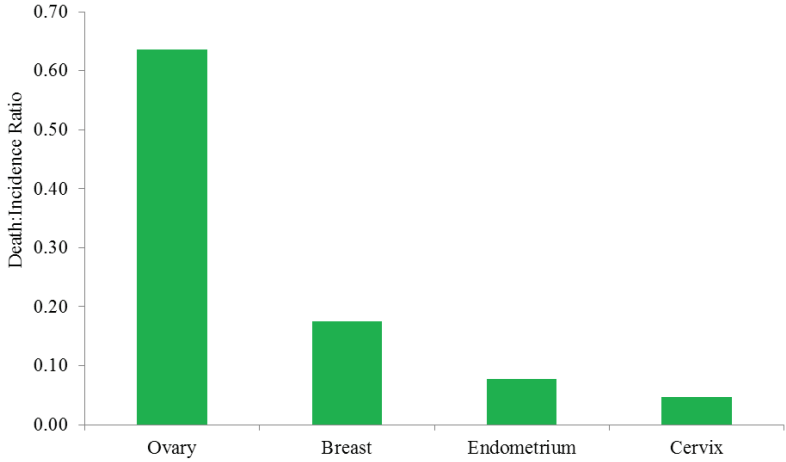

FIGURE 1-3 The ratio between the death and incidence rates for ovarian, breast, endometrial, and cervical cancers per 100,000 women in the United States, 2008–2012.
SOURCE: Howlader et al., 2015.

Trends

The incidence of ovarian cancer has declined slightly since the mid-1970s, when the incidence was approximately 16 new cases per 100,000 women (Howlader et al., 2015). Mortality from ovarian cancer has also declined—from 9.8 deaths per 100,000 women in 1975 to 7.4 deaths per 100,000 women in 2012. However, the decline in mortality is relatively small when compared to reductions in death rates achieved for most other female gynecological cancers and for breast cancer in women. For example, the death rate from breast cancer fell by one-third between 1975 and 2012, from 31.4 deaths per 100,000 women to 21.3 deaths per 100,000, and the death rate from cervical cancer dropped by more than half during that same period, from 5.6 deaths per 100,000 women to 2.3 deaths per 100,000.

Among women who were diagnosed with ovarian cancer between 1975 and 1977, only 36 percent lived 5 years or more, while nearly half (46 percent) of women diagnosed with ovarian cancer between 2005 and 2007 lived at least 5 years beyond their diagnosis (Howlader et al., 2015). However, that improvement in survival rates was driven primarily by improvements in survival among white women; survival rates decreased (from 42 to 36 percent) over the same period for black women (ACS, 2015; also see section Race and Ethnicity later in this chapter).

Stage Distribution

Ovarian cancer's high mortality and low survival rates can be attributed in part to the fact that it is rarely diagnosed at an early stage. Indeed, 60 percent of women are diagnosed with advanced disease, when the cancer has already spread beyond the ovary to distant organs or lymph nodes (Howlader et al., 2015). In comparison, as seen in Figure 1-4, other female cancers are more commonly diagnosed during the localized or regional stages.

The relatively late stage of diagnosis for ovarian cancer is particularly important because survival is highly correlated with the stage at diagnosis (see Figure 1-5). While the 5-year survival rate is 45.6 percent overall, it is substantially higher for women diagnosed while the cancer is still at the localized stage (92.1 percent) or the regional stage (73.2 percent), and it is substantially lower for women diagnosed at the distant stage (28.3 percent) (ACS, 2015; Howlader et al., 2015). Survival is lowest among women who receive an unstaged ovarian cancer diagnosis (22.9 percent).

White and black women show similar patterns of stage distribution (see Figure 1-6). However, there is a difference in stage of diagnosis in women

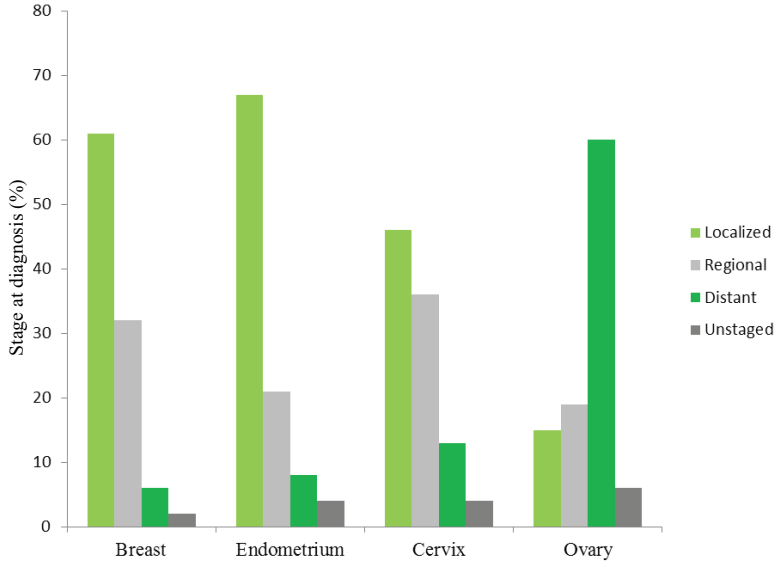

FIGURE 1-4 Distribution (percentage) of stage of diagnosis for cancers of the breast, endometrium, cervix, and ovary among U.S. women, 2005–2011.
SOURCE: Howlader et al., 2015.

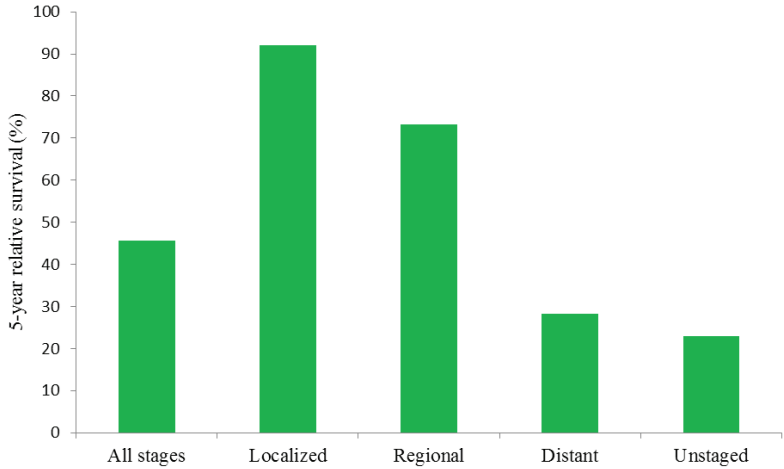

FIGURE 1-5 Five-year relative survival (percentage) from ovarian cancer by stage at diagnosis among U.S. women, 2005–2011.
SOURCE: Howlader et al., 2015.

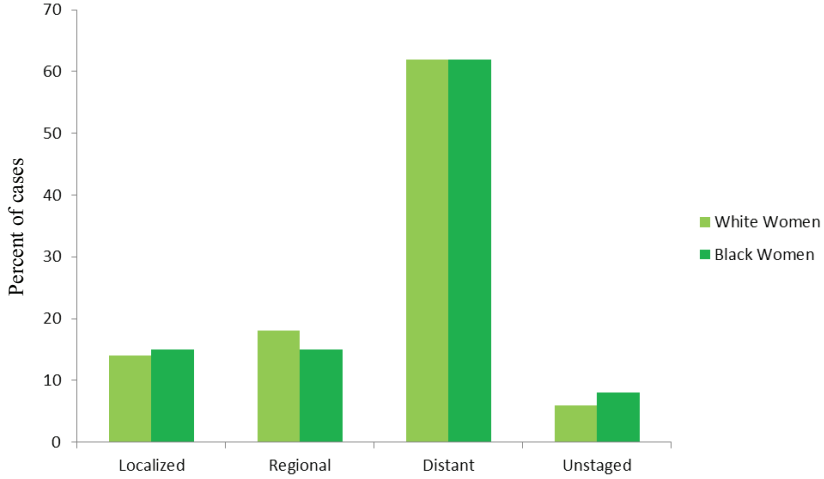

FIGURE 1-6 Stage distribution (percentage of cases) at diagnosis among white and black U.S. women diagnosed with ovarian cancer, 2003–2009.
SOURCE: Howlader et al., 2015.

of different ages, with women younger than age 65 tending to be diagnosed at earlier stages than women older than age 65 (see Figure 1-7).

Age

Ovarian cancer incidence increases with age, with a sharp increase in the rate beginning in the mid-40s (see Figure 1-8). From 2008 to 2012, nearly 88 percent of all new cases of ovarian cancer occurred among women ages 45 and older, with 69 percent of cases among women ages 55 and older, and the average age at diagnosis was 63 years. A half-century ago, most cases occurred among women between the ages of 35 and 63, and the average age at diagnosis was 48.5 years (Munnell, 1952).While the age-adjusted incidence rate for ovarian cancer among all women is nearly 12 cases per 100,000 women, the rate varies sharply with age, with women younger than age 65 having an incidence rate of 7.5 cases per 100,000 women while women 65 years old and older have an incidence rate of more than 42 cases per 100,000 women (Howlader et al., 2015).

Mortality rates also increase sharply with age. The death rate for women aged 65 and older is approximately 13 times that of women less than age 65 (see Figure 1-9). Furthermore, while mortality rates have de-

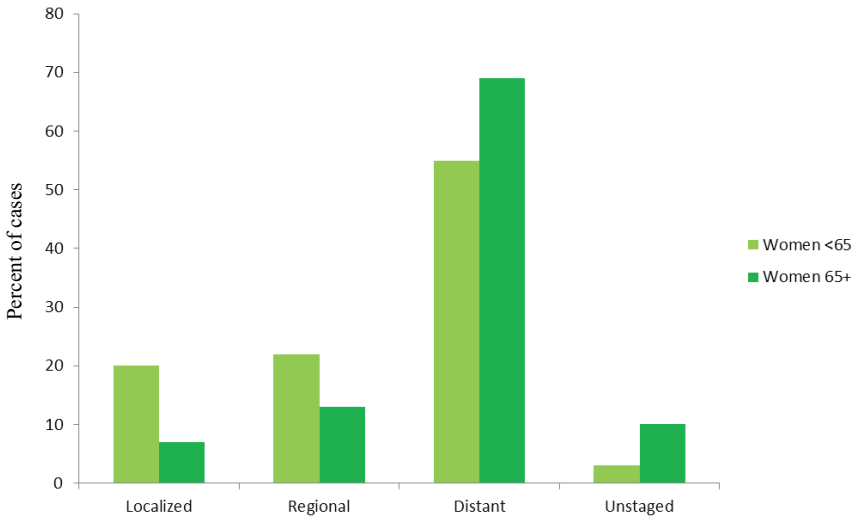

FIGURE 1-7 Stage distribution (percentage of cases) at diagnosis among women diagnosed with ovarian cancer by age, 2003–2009.
SOURCE: Howlader et al., 2015.

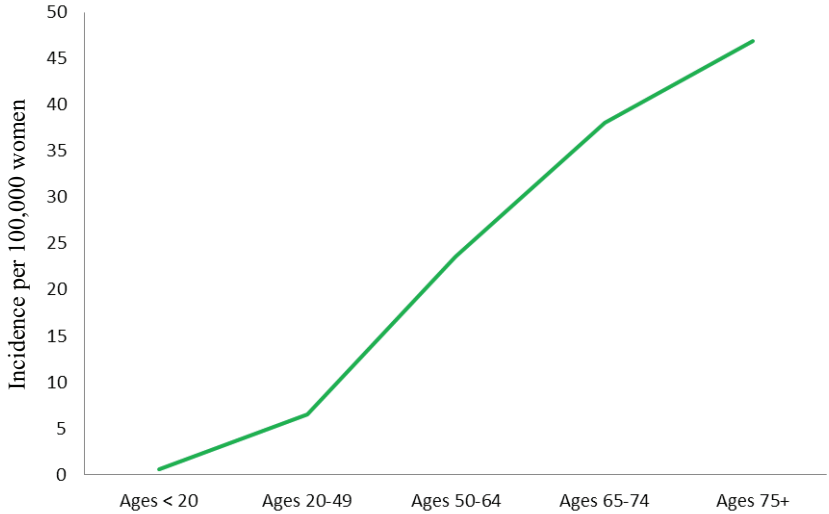

FIGURE 1-8 Age-adjusted incidence of ovarian cancer per 100,000 women in the United States by age group.
SOURCE: SEER Program, 2015.

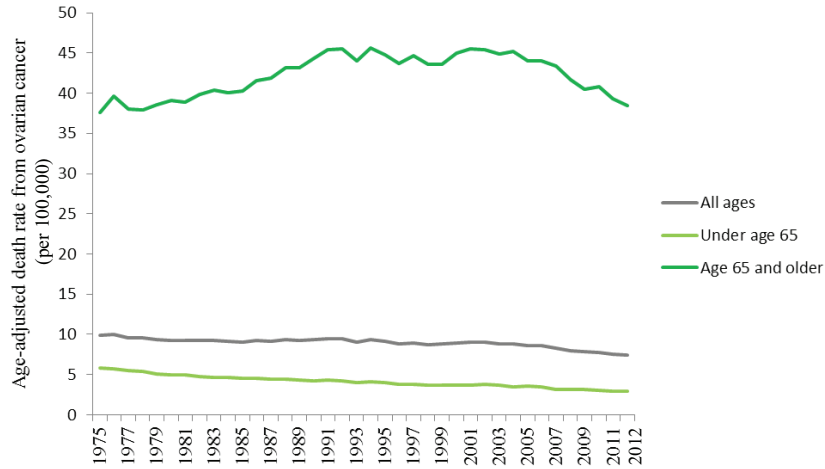

FIGURE 1-9 Trends in age-adjusted death rates from ovarian cancer per 100,000 women in the United States by age group, 1975–2012.
SOURCE: Howlader et al., 2015.

clined overall in the past 40 years, most of this decline is attributable to decreases in mortality among women diagnosed with ovarian cancer less than age 65 (ACS, 2015; Howlader et al., 2015).

Race and Ethnicity

The patterns of ovarian cancer incidence and mortality differ substantially among women of different races and ethnic backgrounds (see Figure 1-10). Whites have the highest incidence of ovarian cancer, followed by Hispanics, American Indian/Alaska Natives, blacks, and Asian/Pacific Islanders (ACS, 2015; Howlader et al., 2015; Singh et al., 2014). The 5-year survival rate is highest among Asian/Pacific Islanders, followed by Hispanics, whites, American Indian/Alaska Natives, and blacks, while mortality rates are highest among whites, followed by blacks, Hispanics, American Indian/Alaska Natives, and Asian/Pacific Islanders. A particularly dramatic contrast can be seen between black and Asian/Pacific Islander women. While the two groups are similar in having low incidence rates, black women have the second-highest mortality rates and the lowest survival rates, while Asian/Pacific Islanders have the lowest mortality and the highest survival rates. The incidence of ovarian cancer, particularly HGSC, is higher than average in women of Ashkenazi Jewish ancestry, in part because of the higher prevalence of deleterious mutations in cancer-predisposition genes such as *BRCA1* and *BRCA2* among these women (ACS, 2015; Moslehi et al., 2000).

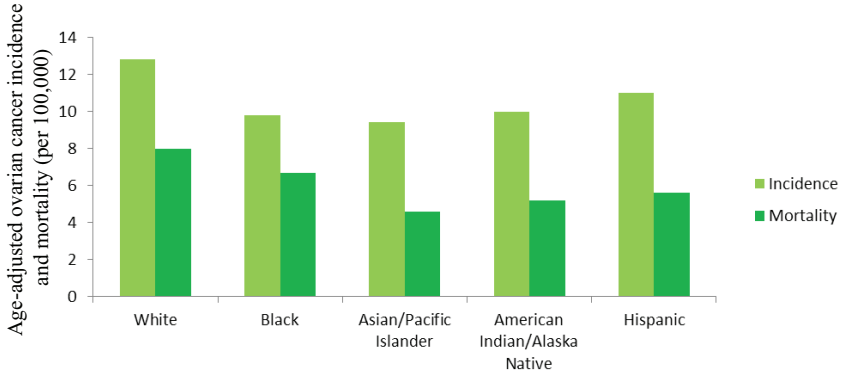

FIGURE 1-10 Age-adjusted ovarian cancer incidence and mortality per 100,000 U.S. women by race and ethnicity, 2008–2012.
SOURCE: Howlader et al., 2015.

Furthermore, the variations in the incidence rates of ovarian cancer by race and ethnicity change as women age (see Figure 1-11). For example, whites and Asian/Pacific Islanders have similar incidence rates until around age 50, when their incidence rates begin to diverge. White women aged 45–49 have an age-specific incidence rate of 15.1 cases per 100,000, and Asian/Pacific Islanders of the same age group have a very similar rate of 15.5 cases per 100,000. By contrast, white women aged 80–84 have an incidence rate of 50.8 cases per 100,000, while Asian/Pacific Islanders of the same age group have a dramatically lower rate of 30.1 cases per 100,000.

Historical trends also show considerable variations by race. Between 2003 and 2012, mortality rates decreased significantly among whites and Hispanics, while declines in mortality among blacks, Asian/Pacific Island-

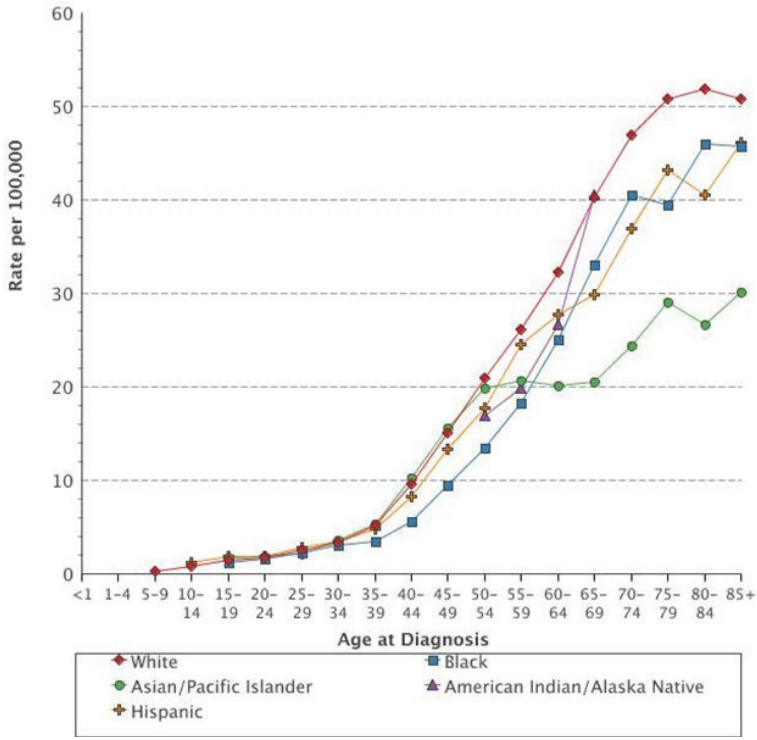

FIGURE 1-11 Age-specific incidence rates of ovarian cancer per 100,000 women in the United States by race/ethnicity and age at diagnosis, 2008–2012.
NOTE: Rates for American Indian/Alaska Natives are only displayed for ages 50 through age 69, because the number of cases in other age groups were less than 16 per age group.
SOURCE: SEER Program, 2015.

ers, and American Indian/Alaskan Natives were not statistically significant (Howlader et al., 2015). Moreover, while survival rates have increased among women overall and among white women since the mid-1970s, survival rates have declined slightly among black women (see Figure 1-12). Furthermore, although black women had higher rates of survival compared to white women and to women overall in 1975, by the mid-1980s survival rates had begun to reverse, such that black women now have lower survival rates than white women and women of all races overall even despite gains in survival among blacks in the 1990s (ACS, 2015).

Geography

In the United States, there are slight geographic variations in ovarian cancer incidence, but these variations are not significant (Howlader et al., 2015; Ries et al., 2007). However, the differences in mortality from state to state are significant. In the United States, from 2008 to 2012 the death rate for ovarian cancer was 7.7 deaths per 100,000 women. During that same period, the age-adjusted death rates by state ranged from a low of 5.3 deaths per 100,000 women in Hawaii to a high of 9.0 deaths per 100,000 women in Oregon (Howlader et al., 2015). Despite the wide variation

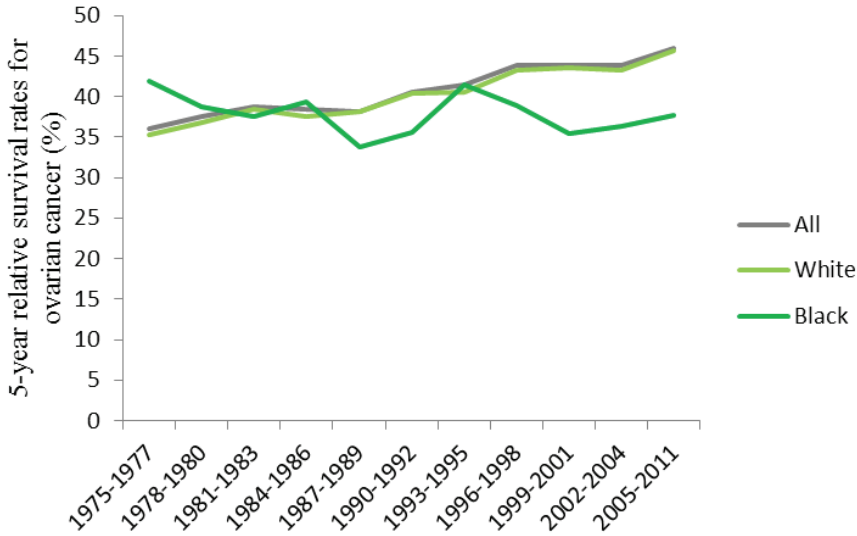

FIGURE 1-12 Trends in 5-year relative survival rates (percentage) for ovarian cancer among U.S. women by race, 1975–2011.
SOURCE: Howlader et al., 2015.

across the states, only Alabama, Oregon, Pennsylvania, and Washington have significantly higher rates, statistically speaking, than the United States as a whole, while only Florida, Hawaii, and Texas have significantly lower rates than the national average.

Ovarian cancer incidence and mortality also vary internationally, with incidence and mortality rates being higher in more developed regions than in less developed regions (Ferlay et al., 2015).

Challenges

Aside from genetics (e.g., the higher proportion of mutations in cancer-predisposition genes among Ashkenazi Jewish women), the reasons behind the racial and ethnic differences in outcomes are unknown, but they might be explained in part by other variables such as differences in access to health care or the quality of that care (Baicker et al., 2005; IOM, 2003, 2012). Similarly, the reasons behind geographic variation in the demographics of ovarian cancer are unknown, and might be explained by other variables such as race and ethnicity (e.g., the higher proportion of Asian and Pacific Islanders in Hawaii) or differences in access to health care or the quality of that care in different geographic regions (Baicker et al., 2005; IOM, 2003, 2012). (See Chapter 4 for more on access and standards of care for women with ovarian cancer.) Overall, as noted previously, reporting on the demographics and epidemiology of ovarian cancer is challenging because of the fact that most of the data sources aggregate the various subtypes, and even when the data are reported by subtype, differences in the grading, classification, and nomenclature of the subtypes create challenges in summarizing and comparing data.

THE LANDSCAPE OF STAKEHOLDERS IN OVARIAN CANCER RESEARCH

Many public and private organizations are involved in funding, supporting, and carrying out ovarian cancer research, and they are involved in a variety of ways. The research is sometimes focused on ovarian cancers exclusively, but it sometimes looks at broader populations (e.g., women with gynecologic cancers). A complete cataloguing of every stakeholder in ovarian cancer research and of their individual efforts is beyond the scope of this report. Instead, this section offers an overview of the wide range of stakeholders and highlights the areas of ovarian cancer research that are getting the most attention and the methods used by stakeholders to communicate about new findings in ovarian cancer research.

Federal Stakeholders

While there are a number of different federal stakeholders in ovarian cancer research, the CDC, the U.S. Department of Defense (DoD), and the NIH (and the NCI in particular) are collectively responsible for the majority of the funding for ovarian cancer research at the federal level. The sections below give an overview of the funding levels and focus areas for these agencies. Where possible, the areas of focus are presented in alignment with the Common Scientific Outline (CSO), an international classification system used by cancer researchers to compare research portfolios. The CSO consists of seven broad areas of interest:

1. Biology;
2. Etiology (causes of cancer);
3. Prevention;
4. Early detection, diagnosis, and prognosis;
5. Treatment;
6. Cancer control, survivorship, and outcomes research; and
7. Scientific model systems (DoD, 2015b).

Centers for Disease Control and Prevention

The CDC conducts and supports studies, often in collaboration with partners, to "develop, implement, evaluate, and promote effective cancer prevention and control practices" (CDC, 2015). In general, the CDC approaches cancer by monitoring cancer demographics (surveillance), by conducting research and evaluation, by partnering with other stakeholders to help translate evidence, and by developing educational materials (CDC, 2015). Most of the CDC's work in ovarian cancer is performed through its Division of Cancer Prevention and Control.[6] Since fiscal year (FY) 2000, the CDC has received about $5 million annually in congressional appropriations to support its Ovarian Cancer Control Initiative. In addition, in 2008 the CDC started receiving funds under Johanna's Law to improve communication with women regarding gynecologic cancers. The CDC's Inside Knowledge[7] campaign works to raise awareness about cervical, ovarian, uterine, vaginal, and vulvar cancers. Between 2010 and 2014, ads produced for the Inside Knowledge campaign were seen or heard around 3.5 million times and were worth a total of $136 million in donated ad value (CDC, 2014).

[6]For more information, see http://www.cdc.gov/cancer/dcpc/about (accessed July 21, 2015).
[7]For more information, see http://www.cdc.gov/cancer/knowledge (accessed September 1, 2015).

U.S. Department of Defense

The DoD's Ovarian Cancer Research Program (OCRP)[8] received congressional appropriations from FY 1997 to FY 2014 totaling $236.45 million and received another $20 million in appropriations for FY 2015 (DoD, 2015a). Since the inception of the DoD OCRP, more than 130 ovarian cancer survivors have taken part in efforts to establish the OCRP's priorities and research award mechanisms, and they have helped choose the research to be funded. From FY 1997 through FY 2013, the OCRP funded 313 awards in a variety of areas (see Figure 1-13). These awards show a focus on biology, treatment, and early detection, diagnosis, and prognosis. OCRP's research priorities include understanding the precursor lesions, microenvironment, and pathogenesis of all types of ovarian cancer; developing and improving the performance and reliability of screening, diagnostic approaches, and treatment; developing or validating models to study initiation and progression; investigating tumor response to therapy; and enhancing the pool of ovarian cancer scientists (DoD, 2015a).

National Institutes of Health

The NCI of the NIH has initiated several activities to advance ovarian cancer research with intramural and extramural funding. In the past, five ovarian cancer–specific specialized programs of research excellence (SPOREs) in the United States conducted ovarian cancer research in early detection, imaging technologies, risk assessment, immunosuppression, and novel therapeutic approaches (NCI, 2015e). The NCI currently lists four active SPOREs for ovarian cancer.

The NCI is involved in ovarian cancer research in a variety of other ways. For example, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) is trying to understand the molecular basis of cancer in order to help improve the diagnosis, treatment, and prevention of cancer (NCI, 2015b). To accomplish these goals, CPTAC is using the data collected by The Cancer Genome Atlas (TCGA) analysis of ovarian tumors. The NCI has also supported a follow-up of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to analyze the biological material and risk factor information in order to better understand the risks and identify early biomarkers, including biomarkers for ovarian cancers. (See Chapter 3 for more on the PLCO Cancer Screening Trial.)

[8]For more information, see http://cdmrp.army.mil/ocrp (accessed July 21, 2015).

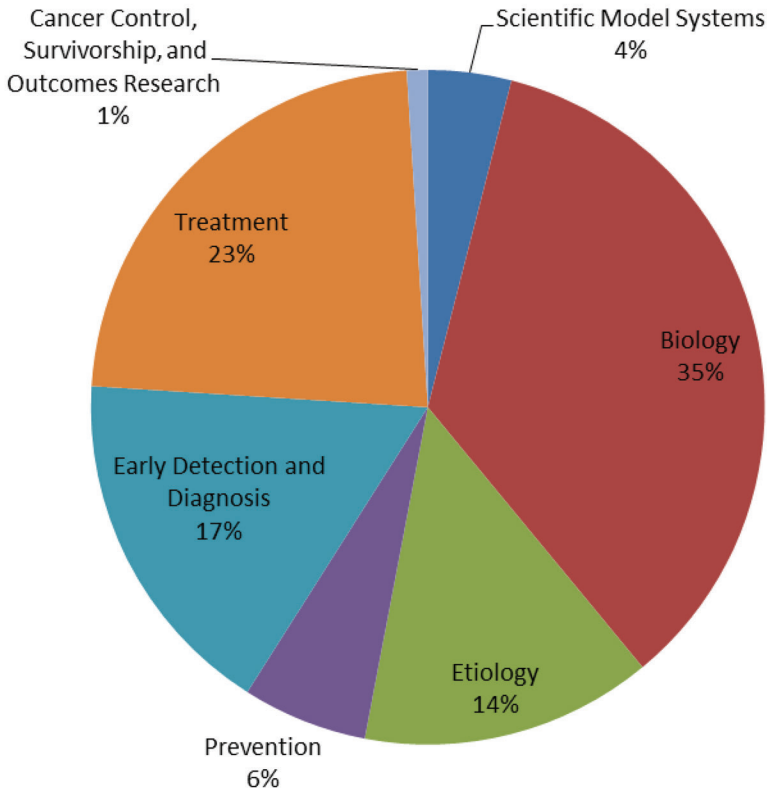

FIGURE 1-13 Areas of ovarian cancer research funded by OCRP, FY 1997–2011. SOURCE: DoD, 2015b.

Overall, the NCI supported $100.6 million in research[9] related to ovarian cancer in FY 2013 while providing $559.2 million for breast cancer research, $63.4 million for cervical cancer research, and $17.8 million for endometrial cancer research (NCI, 2015g). However, the research projects listed as being related to ovarian cancer are not necessarily limited to ovarian cancer, and they include studies of multiple cancers (including ovarian cancer) or areas of cross-cutting research related to ovarian cancer. Fur-

[9]The NCI notes that "the estimated NCI investment is based on funding associated with a broad range of peer-reviewed scientific activities" (NCI, 2015g). The NCI research portfolio for ovarian cancer may be found at http://fundedresearch.cancer.gov/nciportfolio/search/get?site=Ovarian+Cancer&fy=PUB2013 (accessed December 2, 2015).

thermore, data collected by the DoD[10] through the International Cancer Research Partnership indicates that the funded amount is significantly less when considering only new grants awarded by the NCI each year. Only 52 projects involving ovarian cancer research totaling $33.4 million were started in 2010, 58 new projects totaling $20.4 million in 2011, and 52 new projects totaling $16.3 million in 2012 (ICRP, 2015). Figure 1-14 shows that, like the DoD, the NCI portfolio for ovarian cancer research focuses primarily on treatment, biology, and early detection, diagnosis, and prognosis.

The Office of Cancer Survivorship (OCS),[11] part of the Division of Cancer Control and Population Sciences at the NCI, "works to enhance the quality and length of survival of all persons diagnosed with cancer and to minimize or stabilize adverse effects experienced during cancer survivorship. The office supports research that both examines and addresses the long- and short-term physical, psychological, social, and economic effects of cancer and its treatment among pediatric and adult survivors of cancer and their families" (NCI, 2014).

Figure 1-15 shows the areas of cancer survivorship research expertise at the NCI. As of October 2015, the Division of Cancer Control and Population Sciences had two open funding opportunities for general cancer survivorship research: one focused on the efficacy and impact of care planning, and the other examined the effects of physical activity and weight control interventions on cancer prognosis and survival (NCI, 2015a). Neither of these grant opportunities specified a focus on ovarian cancer survivorship.

Private Stakeholders

A wide variety of private stakeholders are engaged in ovarian cancer research, including professional societies, advocacy organizations, women's health groups, and disease-specific foundations. In some cases, the organization specifically focuses on ovarian cancer and ovarian cancer research. However, many others focus on cancer or women's health broadly (e.g., the American Cancer Society and the American Congress of Obstetricians and Gynecologists). Overall, private funders of ovarian cancer research tend to focus funding on biology and treatment, with very little funding directed toward the etiology of ovarian cancer or survivorship issues.

Private stakeholders can support young researchers with grant funding; provide training and educational opportunities; encourage collabora-

[10] Personal communication, Patricia Modrow, data assembled by the U.S. Department of Defense Ovarian Cancer Research Program, January 16, 2015.

[11] For more information about the OCS, see http://cancercontrol.cancer.gov/ocs (accessed May 15, 2015).

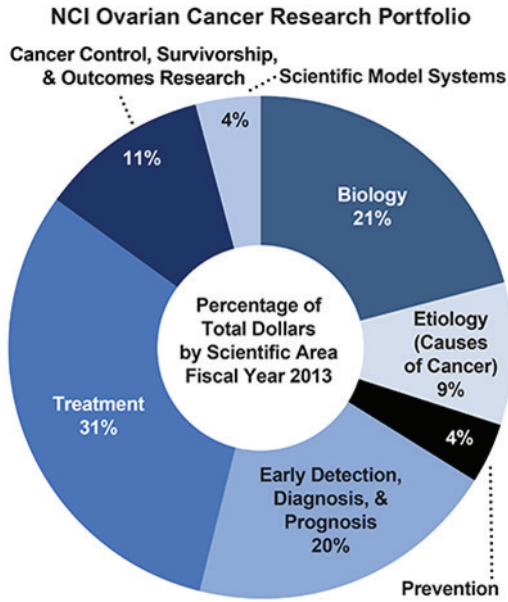

FIGURE 1-14 Areas of ovarian cancer research funded by the NCI.
SOURCE: NCI, 2013.

tive, transdisciplinary efforts; and engage consumers, survivors, and their families. Examples of previous and current efforts by individual private stakeholders include

- The Health, Empowerment, Research, and Awareness Women's Cancer Foundation awarded the Sean Patrick Multidisciplinary Collaborative Grant for cross-disciplinary projects to allow scientists to come together and test ideas that may not be fundable by other agencies (HERA, 2015).
- The Marsha Rivkin Center for Ovarian Cancer Research awards Bridge Funding Awards to researchers who are close to fundable grant scores for the DoD or the NIH but require additional data to ensure a successful resubmission (Rivkin Center, 2015).
- The Ovarian Cancer Research Fund (OCRF) provides funding to researchers at all stages of their careers; OCRF awards include funding for recent graduates, newly independent researchers who are building laboratories, and senior researchers working on collaborative projects (OCRF, 2015).

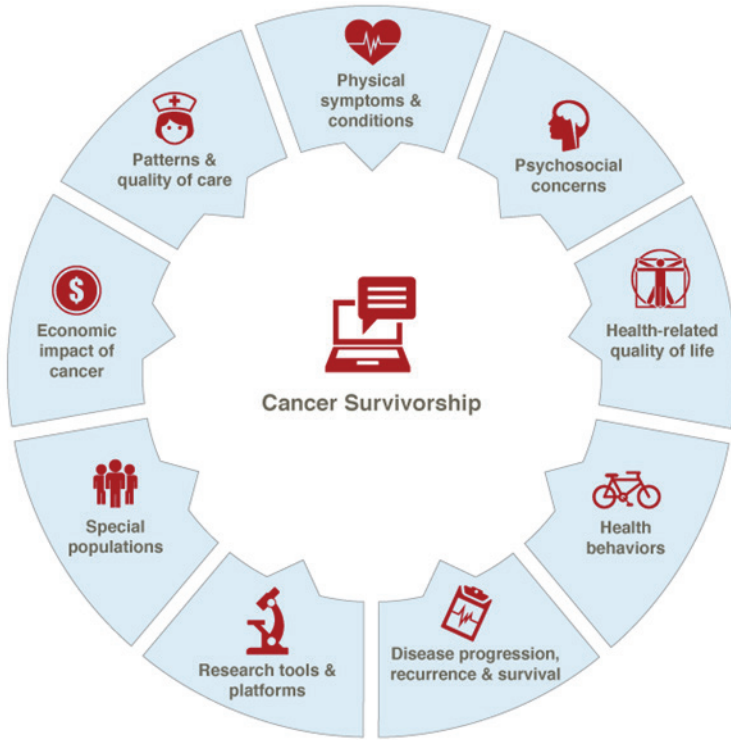

FIGURE 1-15 Expertise areas for cancer survivorship research at the NCI. SOURCE: NCI, 2015c.

- The Society of Gynecologic Oncology (SGO) released *Pathways to Progress in Women's Cancer* in 2011, a research agenda based on discussions of working groups at a 2010 research summit. One working group focused on ovarian cancers, and the report provides short-term, intermediate, and long-term research priorities (SGO, 2011).
- The Honorable Tina Brozman Foundation for Ovarian Cancer Research (also known as Tina's Wish) funds research specifically in the early detection and prevention of ovarian cancer and also supports a consortium to advance such research (Tina's Wish, 2015).

The Role of Advocacy in Ovarian Cancer Research

Advocacy has positively affected ovarian cancer research, public knowledge, and awareness. Many different types of people play the role of

advocate—women with ovarian cancer, partners, family members, health care professionals, and activists—and their advocacy efforts range from the individual, patient level to the societal level, but all of these different efforts have had effects on funding efforts, policy change, and the direction of research.

Patients self-advocate by taking active roles in their own care. Researchers have recognized this concept of self-advocacy as an important part of patient-centered care, and it has been described as "a distinct type of advocacy in which an individual or group supports and defends their interests either in the face of a threat or proactively to meet their needs" (Hagan and Donovan, 2013, p. 3). However, despite claims that self-advocacy may improve quality of life, health care use, and symptom management, these potential effects have not been adequately studied.

Nurses can serve as advocates for patients by protecting patients' rights, incorporating patients' beliefs and values into their care plans, and respecting the autonomy of the patient to ensure access to quality care (Temple, 2002). Advocacy groups provide education, information, and personal support to patients, family caregivers, and the general public. Many advocacy groups also use lobbying efforts to influence policy, including the direction of research and funding.

Large-scale advocacy efforts have arguably had a great impact on cancer research and funding. In the late 1990s, survivors advocated for wider recognition of early-stage ovarian cancer symptoms. Until that time, physicians and medical textbooks had claimed that women did not experience symptoms until advanced stages of disease (Twombly, 2007). Johanna's Law is considered a victory of advocacy groups' lobbying efforts. Furthermore, Congress has appropriated funds for ovarian cancer research and education programs since FY 1997. The establishment and unified efforts of national advocacy organizations are partially responsible for the significant funding increases in the intervening years (Temple, 2002).

Advocacy groups have also been integral to the advancement of ovarian cancer research through their participation in the design and administration of studies (Armstrong et al., 2014; Holman et al., 2014). The scientific literature emphasizes the importance of patient advocates in patient-centered research, citing examples of the collaboration between researchers and patient advocates in research studies (Armstrong et al., 2014; Holman et al., 2014; Staton et al., 2008).

Several large advocacy groups at the national and international levels focus on ovarian cancer. For example, the Ovarian Cancer National Alliance (OCNA), a national advocacy organization, has among its activities the Survivors Teaching Students: Saving Women's Lives® program, which is aimed at educating caregivers and medical, nursing, and other professional

students about the early signs and symptoms of ovarian cancer. Recently, OCNA spearheaded the formation of the first congressional Ovarian Cancer Caucus with the support of Rosa DeLauro (D-CT) and Sean Duffy (R-WI). The first meeting was held on September 29, 2015, in Washington, DC. The National Ovarian Cancer Coalition (NOCC), another national advocacy organization, funds the Teal Initiative to improve education and awareness. NOCC also supports specific research in ovarian cancer and provides survivor support, primarily through its Faces of Hope program, which is "dedicated to improving the quality of life for women affected by ovarian cancer, as well as providing support for their loved ones and caregivers" (NOCC, 2014). At the international level, the charity Ovarian Cancer Action encourages collaboration among ovarian cancer researchers around the world. Half of its funds go to the Ovarian Cancer Action Research Centre in the United Kingdom, which exclusively supports "research that can be translated into meaningful outcomes for real women in real life" (Ovarian Cancer Action, 2015). In addition, every few years Ovarian Cancer Action hosts an international forum to bring researchers together to share information, inspire collaboration, and develop white papers. In 2011 the forum developed the paper *Rethinking Ovarian Cancer: Recommendations for Improving Outcomes*, which outlined recommendations for improving outcomes for women with ovarian cancer (Vaughan et al., 2011). A number of other advocacy groups work at the local and national levels to support research in ovarian cancer.

The Role of Consortia and Collaboration in Ovarian Cancer Research

Because of the relative rarity of ovarian cancers, especially when subdivided according to subtypes, collaborative research efforts are necessary in order to collect sufficient data for statistically significant results. Many consortia and multisite studies have evolved to promote the sharing of biospecimens, clinical data, and epidemiologic data in order to ensure sufficient sample sizes in studies. These consortia and collaborations operate at both the national and international levels. Common uses of consortia include carrying out research on the genetic and nongenetic risk factors of developing ovarian cancers, studying mechanisms of disease relapse and resistance, and identifying newer therapies (AOCS, 2015; COGS, 2009; NRG Oncology, 2015; OCAC, 2015; OCTIPS, 2015). Furthermore, groups will often team together in coalitions to promote transdisciplinary research and also to promote the translation and dissemination of information. For example, in 2015, OCNA, NOCC, and OCRF provided funding for the Stand Up To Cancer (SU2C) Dream Team for ovarian cancer. This team will bring together experts in DNA repair, translational investigators, and

clinicians "to create new programs in discovery, translation, and clinical application, while cross-fertilizing and educating researchers at all levels to enhance collaboration and catalyze translational science" (SU2C, 2015).

Consortia and coalitions have had clear, measureable impacts on the research base for ovarian cancers. For example, as a result of the Collaborative Oncological Gene-environment Study (COGS), 14 new markers for risk of ovarian cancer were identified (only 8 had been known before COGS) (COGS, 2014). Based on the work of this coalition, TCGA researchers completed a detailed analysis of ovarian cancer, which confirmed that mutations in the *TP53* gene (which encodes a protein that normally suppresses tumor development) are present in nearly all HGSCs (Bell et al., 2011). The analysis also examined gene expression patterns and identified signatures that correlate with survival outcomes, affirmed four subtypes of HGSCs, and identified dozens of genes that might be targeted by gene therapy (NIH, 2011, 2015b).

NCI's National Clinical Trials Network

In 1955 the NCI established the Clinical Trials Cooperative Group Program. As the science of cancer treatment was evolving, researchers realized that collaborative efforts were necessary to accrue sufficient numbers for clinical trials in order to more rapidly compare the value of new therapies to existing standards of care, particularly for the use of chemotherapy in the treatment of solid tumors (DiSaia et al., 2006; IOM, 2010b). The work of the cooperative groups led to advances in the treatment of women with ovarian cancer specifically, including a demonstration of the value of adding paclitaxel to cisplatin, confirmation of the value of cytoreductive surgery, and a demonstration of the value of carboplatin for late-stage ovarian cancers (IOM, 2010b). The groups have also studied issues related to the quality of life and the prevention of ovarian cancer. Between 1970 and 2005, clinical trials of the Gynecologic Oncology Group (GOG) alone included approximately 35,000 women with ovarian cancer (DiSaia et al., 2006).

In 2014, based in part on the IOM report *A National Cancer Clinical Trials System for the 21st Century*, the NCI transformed the cooperative group program into the new National Clinical Trials Network (IOM, 2010b, 2011, 2013b; NCI, 2015f). This reorganization consolidated nine cooperative groups into five new groups:

- The Alliance for Clinical Trials in Oncology;
- The ECOG-ACRIN Cancer Research Group (a merger of two cooperative groups: the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network);

- NRG Oncology (a merger of three cooperative groups: the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the GOG);
- The Southwest Oncology Group; and
- The Children's Oncology Group (NCI, 2015f).

PREVIOUS WORK AT THE INSTITUTE OF MEDICINE

The IOM has a long history of producing reports related to various aspects of cancer care, and many of them are directly relevant to this current study. This section describes some examples of previous IOM work that is related to the work of this committee.

Prevention and Early Detection

In 2005 the IOM report *Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis* (IOM, 2005) recommended the development of tools to identify the women who would benefit most from breast cancer screening based on "individually tailored risk prediction techniques that integrate biologic and other risk factors." The report also called for the development of tools that "facilitate communication regarding breast cancer risk to the public and to health care providers." In addition, the report called for more research on breast cancer screening and detection technologies, including research on various aspects of technology adoption (e.g., monitoring the use of technology in clinical practice).

A 2007 IOM report, *Cancer Biomarkers*, offered recommendations on the methods, tools, and resources needed to discover and develop biomarkers for cancer; guidelines, standards, oversight, and incentives needed for biomarker development; and the methods and processes needed for clinical evaluation and adoption of such biomarkers (IOM, 2007a). Specific recommendations from the report included establishing international consortia to generate and share data, supporting high-quality biorepositories of prospectively collected samples, and developing criteria for conditional coverage of new biomarker tests. Subsequently, in 2010, an IOM report, *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease*, outlined a framework for the evaluation of biomarkers (IOM, 2010a).

Genetics

In *Initial National Priorities for Comparative Effectiveness Research* (IOM, 2009), the committee offered two priorities that are relevant to ovarian cancer genetics: "Compare the effectiveness of adding informa-

tion about new biomarkers (including genetic information) with standard care in motivating behavior change and improving clinical outcomes" and "Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist" (IOM, 2009, p. 4).

In 2007, the IOM's National Cancer Policy Forum hosted a workshop on cancer-related genetic testing and counseling. According to the published summary of that workshop, participants observed that "genetic testing and counseling are becoming more complex and important for informing patients and families of risks and benefits of certain courses of action, and yet organized expert programs are in short supply. The subject matter involves not only the scientific and clinical aspects but also workforce and reimbursement issues, among others" (IOM, 2007b)

Clinical Trials

The 2005 IOM report on breast cancer detection called for public health campaigns and for improved information and communication about the value of participation in clinical trials (including the participation of healthy individuals).

A 2010 report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program* (IOM, 2010b), called for the restructuring of the NCI Cooperative Group Program and set four goals:

1. Improve the speed and efficiency of the design, launch, and conduct of clinical trials (e.g., improve collaboration among stakeholders);
2. Incorporate innovative science and trial design into cancer clinical trials (e.g., support standardized central biorepositories, develop and evaluate novel trial designs);
3. Improve the means of prioritization, selection, support, and completion of cancer clinical trials (e.g., develop national unified standards); and
4. Incentivize the participation of patients and physicians in clinical trials (e.g., develop electronic tools to alert clinicians to available trials for specific patients, encourage eligibility criteria to allow broad participation, cover cost of patient care in trials).

Palliative and End-of-Life Care

Improving Palliative Care for Cancer (IOM, 2001) called for incorporating palliative care into clinical trials. The report also noted that infor-

mation on palliative and end-of-life care is largely absent from materials developed for the public about cancer treatment, and the committee recommended strategies for disseminating information and improving education about end-of-life care. The report recommended that the NCI require comprehensive cancer centers to carry out research in palliative care and symptom control and that the Health Care Finance Administration (now the Centers for Medicare & Medicaid Services) fund demonstration projects for service delivery and reimbursement that integrate palliative care throughout the course of the disease.

Dying in America (IOM, 2015) noted that palliative care can begin early in the course of treatment, in conjunction with treatment, and can continue throughout the continuum of care. The report further observed that "a palliative approach can offer patients near the end of life and their families the best chance of maintaining the highest possible quality of life for the longest possible time" (IOM, 2015, p. 1).

Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis (IOM, 2013a) addressed the delivery of cancer care, including palliative and end-of-life care. The study called for providing patients and their families with understandable information about palliative (and other) care and recommended that "the cancer care team should provide patients with end-of-life care consistent with their needs, values, and preferences" (IOM, 2013a, p. 9).

Communication and Survivorship

From Cancer Patient to Cancer Survivor (IOM, 2006) called for actions to raise awareness about the needs of cancer survivors, including the establishment of cancer survivorship as a distinct phase of cancer care. In 2008, the IOM report *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs* (IOM, 2008) recommended that facilitating effective communication between patients and care providers, identifying psychosocial health needs, and engaging and supporting patients in managing their illnesses should all be considered as part of the standard of care. The report emphasized the importance of educating patients and their families and of enabling patients to actively participate in their own care by providing tools and training in how to obtain information, make decisions, solve problems, and communicate more effectively with their health care providers. The report further called for the government to invest in a large-scale demonstration and evaluation of various approaches to the efficient provision of psychosocial health care.

Women's Health Research (IOM, 2010c) found that there are many barriers to the translation of research findings in general and that some have aspects that are "peculiar to women." The committee recommended

specific research on how to translate research findings on women's health into clinical practice and public health policies.

Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis (IOM, 2013a) called for providing patients and their families with "understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of the total and out-of-pocket costs of cancer care." The report further called for the development of decision aids to be made available through print, electronic, and social media; for the formal training of cancer care team members in communication; for the communication of relevant and personalized information at key decision points along the continuum of cancer care; and for consideration of patients' individual needs, values, and preferences when developing a care plan, including end-of-life care. The report also called for the identification and public dissemination of evidence-based information about cancer care practices that are unnecessary or for which the harm may outweigh the benefits.

OVERVIEW OF THE REPORT

This chapter has provided an overview of the study charge and the committee's approach to its work. It has also provided an introduction to the challenges in ovarian cancer research, to defining and classifying ovarian cancers, to the patterns and demographics of the disease, and to the landscape of stakeholders in ovarian cancer research. The remaining chapters follow the research framework outlined in Figure 1-1.

Chapter 2 describes the current state of the science in the biology of ovarian cancers, thus providing a foundation for the descriptions of most of the other ovarian cancer research covered in this report. This background includes information about the characteristics of specific ovarian carcinomas, the role of the tumor microenvironment, and experimental model systems.

Chapter 3 builds on this to discuss research on the prevention and early detection of ovarian cancers. On the topic of risk assessment, the chapter includes discussions of a wide range of genetic and nongenetic risk factors for the development of an ovarian cancer, risk-prediction models, and genetic testing. Concerning prevention, both surgical and nonsurgical prevention strategies are discussed. And on the topic of early detection, the chapter has descriptions of various approaches to identifying ovarian cancers earlier, including biomarkers and imaging techniques, and a discussion of the challenges in performing screening in both general and high-risk populations.

Chapter 4 describes the research base for the diagnosis and treatment of women newly diagnosed with ovarian cancer as well as for women with

relapsed ovarian cancer. The chapter outlines research on current standards of care and also explores the development of novel therapeutics such as anti-angiogenics, poly ADP ribose polymerase (PARP) inhibitors, and immunotherapy. Later, the chapter discusses issues of clinical trial development and use as they relate specifically to research in ovarian cancer.

Chapter 5 discusses research on survivorship and management issues along the entire care continuum from diagnosis to end of life. Furthermore, women who are at a high risk for developing cancer (sometimes referred to as "previvors") may have psychosocial needs of their own that should be studied. Overall, research that focuses specifically on survivorship and management issues in ovarian cancer is scarce; it may thus be necessary to apply research from broader studies of survivorship to women with ovarian cancer. The chapter discusses the research base for the unique issues of survivorship and management for women with ovarian cancer and their families, including managing the physical side effects of treatment, addressing unique psychosocial impacts, engaging women in their own self-care, and addressing end-of-life concerns.

Chapter 6 summarizes the findings and conclusions of the previous chapters in order to provide a cohesive set of recommendations for prioritizing research on ovarian cancers in such a way as to have the greatest impact on reducing morbidity and mortality from the disease.

Chapter 7 gives an overview of research on the translation and dissemination of new information to the general public, providers, researchers, policy makers, and others. The chapter reflects on the messages within the previous chapters that are ready to be communicated and identifies potential avenues for communicating these messages.

Finally, the report contains five appendixes. Appendix A contains a list of key acronyms used throughout the report. Appendix B contains a glossary of key terms. Appendix C includes a listing of currently active studies on epithelial ovarian cancer (based on information available through www.ClinicalTrials.gov) in order to give a sense of where emphasis is being placed in future research. Appendix D lists the agendas of the committee's workshops. Appendix E contains the biographical sketches of the committee members and project staff.

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2

The Biology of Ovarian Cancers

An improved understanding of ovarian cancer biology can serve as a foundation for many other types of research and, as such, may ultimately underlie many improvements in the prevention, screening and early detection, diagnosis, and treatment of—and survival from—ovarian cancer. This chapter outlines the current state of the science in the biology of ovarian cancers along with the challenges and opportunities that exist in advancing research in that area. In particular, this chapter provides an overview of the most common types of ovarian cancer, including their origins, pathobiology, and molecular features, and highlights the research tools needed to address knowledge gaps in our understanding of the biology of this heterogeneous group of tumors.

FEATURES OF OVARIAN CARCINOMAS

The ovaries are composed of different cell types, including germ cells, specialized gonadal stromal cells, and epithelial cells. Ovarian cancer can arise from any of these cell types, but ovarian carcinomas (cancers with epithelial differentiation) make up the majority of ovarian cancers and are responsible for most ovarian cancer–related deaths (Kurman, 2013). The major subtypes of ovarian carcinomas include high-grade serous carcinoma (HGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), low-grade serous carcinoma (LGSC), and mucinous carcinoma (MC). Pathologists classify ovarian carcinomas into these different subtypes based largely on their appearance under the microscope.

High-Grade Serous Carcinoma

HGSC is the most common type of ovarian cancer. HGSCs account for roughly 70 to 74 percent of ovarian carcinomas, and fewer than 5 percent of HGSCs are diagnosed at Stage I (when the disease is confined to the ovaries) (Braicu et al., 2011; Seidman et al., 2004). HGSC tends to present in women much later than LGSC, with the average age of presentation for HGSC—60 years—about 10 years more than the average age for LGSC. Pathologic examinations of HGSCs usually find papillary or solid growth with slit-like spaces, with the tumor cells characterized by abnormal cell nuclei, variability in size and shape, and abundant cell proliferation. HGSCs typically present with a widely disseminated disease that may include sizable masses in the ovaries, omentum, and other intra-abdominal locations, with or without ascites. HGSCs are genetically unstable, which may be due to frequent mutations in the *TP53*, *BRCA1*, and *BRCA2* tumor suppressor genes. Because HGSCs usually present at an advanced stage, the earliest events of HGSC tumorigenesis have been elusive. However, data suggest that a substantial portion of HGSCs originate from the epithelium of the fallopian tube rather than of the ovary (discussed in detail later in this chapter).

Endometrioid Carcinoma

Almost half of ovarian ECs present at Stage I, and, of these, around 15 percent involve both ovaries (Gilks et al., 2008). The prognosis of patients with EC is generally favorable, largely because women with Stage I disease tend to have excellent outcomes (Storey et al., 2008). However, the overall 5-year survival of patients presenting with EC at a higher stage is poor (Storey et al., 2008). Along with CCC (described below), EC is one of the two major types of ovarian carcinoma with a well-defined association with endometriosis (ectopic endometrial tissue) (DePriest et al., 1992; Erzen et al., 2001; Yoshikawa et al., 2000). Around 5 percent of ovarian ECs are associated with synchronous uterine EC at the time of diagnosis (Soliman et al., 2004; Zaino et al., 2001). In these cases, it can be challenging for pathologists to determine, based solely on morphological criteria, whether the endometrial and ovarian tumors represent two independent primary carcinomas or a single primary cancer arising in one organ and metastasizing to the other. Whether it is one or the other distinction has significant implications for both therapy and prognosis, as the outcome is expected to be favorable with two early-stage primary cancers, while the prognosis of an EC that originated in the uterus and then metastasized to one or both ovaries is significantly worse (Soliman et al., 2004; Zaino et al., 2001). Several genes are characteristically mutated in ECs, including

CTNNB1, *PIK3CA*, *KRAS*, *ARID1A*, *PTEN*, and *PPP2R1A* (McConechy et al., 2014). *CTNNB1* mutations are very common in ECs but rare in all of the other major ovarian carcinoma subtypes. In contrast, genes such as *PIK3CA* and *ARID1A* are frequently mutated in both EC and CCC.

Clear Cell Carcinoma

CCCs are so named because the tumor cells typically have abundant clear cytoplasm because of the presence of intracytoplasmic glycogen. Although nearly half of CCCs are diagnosed at Stage I, several studies have noted a relatively unfavorable prognosis for women with these tumors (Anglesio et al., 2011; Jenison et al., 1989; Tammela et al., 1998). As noted previously, CCC is the other major type of ovarian carcinoma that is associated with endometriosis. Researchers have observed several growth patterns for CCCs (e.g., solid, papillary, and tubulocystic), with many CCCs arising in association with cysts or with benign tumors known as clear cell adenofibromas. CCCs that arise from adenofibromas are less likely to be associated with endometriosis than cystic CCCs (Veras et al., 2009). Approximately 50 percent of CCCs contain mutations in *ARID1A*, and around 36 percent of CCCs harbor mutations of *PIK3CA* (Jones et al., 2010; Matsumoto et al., 2015). CCCs also have mutations in *PPP2R1A*, *PTEN*, *KRAS*, and *TP53*, but at a lower frequency (Cho and Shih, 2009; McConechy et al., 2011; I. M. Shih et al., 2011).

Low-Grade Serous Carcinoma

LGSCs are uncommon, and only 10 to 20 percent of them are diagnosed at Stage I (Bell, 2014; Bodurka et al., 2012; Malpica et al., 2004). In a recent series from a large single-institution registry, only 2 percent of LGSCs were Stage I at diagnosis (Gershenson et al., 2015). Although LGSCs generally display more indolent behavior than HGSCs, they are relatively more chemoresistant (Gourley et al., 2014), and the overall survival rate for women diagnosed with the advanced-stage disease remains poor (Gershenson et al., 2015). LGSCs frequently arise in association with serous borderline tumors (SBTs) and present as palpable masses in one or both ovaries. Histologically, LGSCs are characterized by papillary architecture and cells with low mitotic activity and relatively uniform, small nuclei. Metastases from LGSCs often manifest as small solid nests of tumor cells or as micropapillae surrounded by clear spaces or clefts that invade haphazardly into involved tissue. Despite the similarity in names, LGSCs infrequently progress to HGSCs, and, for the most part, the two types of ovarian carcinomas have non-overlapping mutational patterns (Vang et al., 2009). However, there have been several documented cases of LGSCs

transitioning to an "intermediate grade" and then transitioning to HGSCs (Dehari et al., 2007; Parker et al., 2004; Silva et al., 1997). Characteristic mutations in LGSCs include the mutually exclusive activating mutations of *KRAS* or *BRAF* and activating mutations of *ERBB2* (Tone et al., 2014; Vang et al., 2009).

Mucinous Carcinoma

Although benign mucinous tumors of the ovary represent approximately 12 percent of all ovarian tumors in the Western world, MCs are the least common of the major types of ovarian carcinoma. The carcinoma's stage at diagnosis is the most important prognostic factor for MCs, as patients with Stage I disease have an excellent prognosis, while outcomes for those with advanced-stage disease tend to be very poor (Ledermann et al., 2014; Zaino et al., 2011). Until the 1990s researchers believed that the relative frequency of primary MCs was significantly higher than it is now known to be; in the 1990s and 2000s several studies collectively showed that many ovarian MCs are actually metastases from MCs that arose in other sites, such as the gastrointestinal and biliary tracts or pancreas (Lee and Young, 2003; Riopel et al., 1999; Ronnett et al., 1997; Szych et al., 1999; Vang et al., 2006a,b). Histologically, MCs are characterized by glandular architecture and stratified columnar cells with basally located nuclei and pale-staining mucin in the apical cytoplasm. The cytoplasm tends to become mucin-depleted in high-grade MCs. Differentiating between primary and metastatic MC can be challenging because most MCs display evidence of intestinal-type differentiation. Therefore, it is likely that many previous clinical and molecular analyses of MCs were compromised by the inadvertent misclassification of metastatic adenocarcinoma to the ovaries as primary ovarian MCs (Hart, 2005). *KRAS* and *TP53* mutations are found in roughly half of invasive MCs and frequently co-occur in the same tumors (Rechsteiner et al., 2013). *ERBB2* amplification is found in 19 percent of MCs (Anglesio et al., 2013a). Both *ERBB2* amplification and *KRAS* mutation may be associated with improved survival (Anglesio et al., 2013a). There are few good data on the frequency of other molecular alterations in MCs.

Ovarian Carcinoma Classification and Nomenclature

The classification and nomenclature of ovarian carcinomas has evolved over many decades and may continue to evolve as the understanding of the carcinomas' origin and molecular features becomes more refined. Historically, more than one term has been used for some ovarian carcinoma types, which may have hindered progress in understanding their biology and clini-

cal behavior. For example, the terms "micropapillary serous carcinoma" and "psammocarcinoma" have been used for certain subgroups of LGSCs, and HGSCs have been variably referred to as "serous cystadenocarcinomas" or "papillary serous carcinomas" (or "serous papillary carcinomas"). As mentioned above, many tumors previously classified as MCs are actually ovarian metastases from non-ovarian primaries. Furthermore, the systems that pathologists use to grade ovarian carcinomas have evolved over the past several years and vary with subtype. Pathologists continue to use a three-grade system for ECs; CCCs are not currently assigned a grade (they are considered high grade by default); and the grading of serous carcinomas has changed from three grades to two grades (LGSC versus HGSC). Many tumors previously diagnosed as high-grade EC would be classified as HGSC today. A two-grade system for grading MCs is also gaining favor (Seidman et al., 2011). The changes in tumor classification and nomenclature, while necessary to reflect the evolving understanding of ovarian cancer heterogeneity, have undoubtedly contributed to confusion among pathologists, clinicians, and researchers alike.

TISSUE AND CELL OF ORIGIN OF OVARIAN CARCINOMAS

Despite the fact that most cancers involving the ovaries are called ovarian cancer, many of them may not actually originate in the ovaries (see Figure 2-1). Even cancers that originate in the ovaries may arise from cell types that are not considered intrinsic to normal ovaries (e.g., endometrial- or fallopian tube–type epithelium). The incomplete understanding of the origins of each type of ovarian cancer may impede the development of effective prevention, early detection, and treatment methods. In fact, detecting ovarian cancers early may require looking in locations other than the ovaries themselves, because a growing evidence base suggests that many ovarian carcinomas arise from sites outside the ovaries and spread to the ovaries secondarily.

The Origins of HGSCs

Historically, researchers and clinicians assumed that ovarian carcinomas develop from the ovarian surface epithelium (OSE), primarily because the dominant mass is often found in the ovaries. Precursor lesions were scarce and hard to identify, but periodically tubal carcinoma and dysplasia would be reported as having presented concomitantly with ovarian carcinoma (Woolas et al., 1994). Even so, attention did not shift away from the ovaries and toward the fallopian tubes until Dutch investigators studied the fallopian tubes prophylactically removed from women with a genetic predisposition to ovarian cancer and noted lesions, now called serous tubal

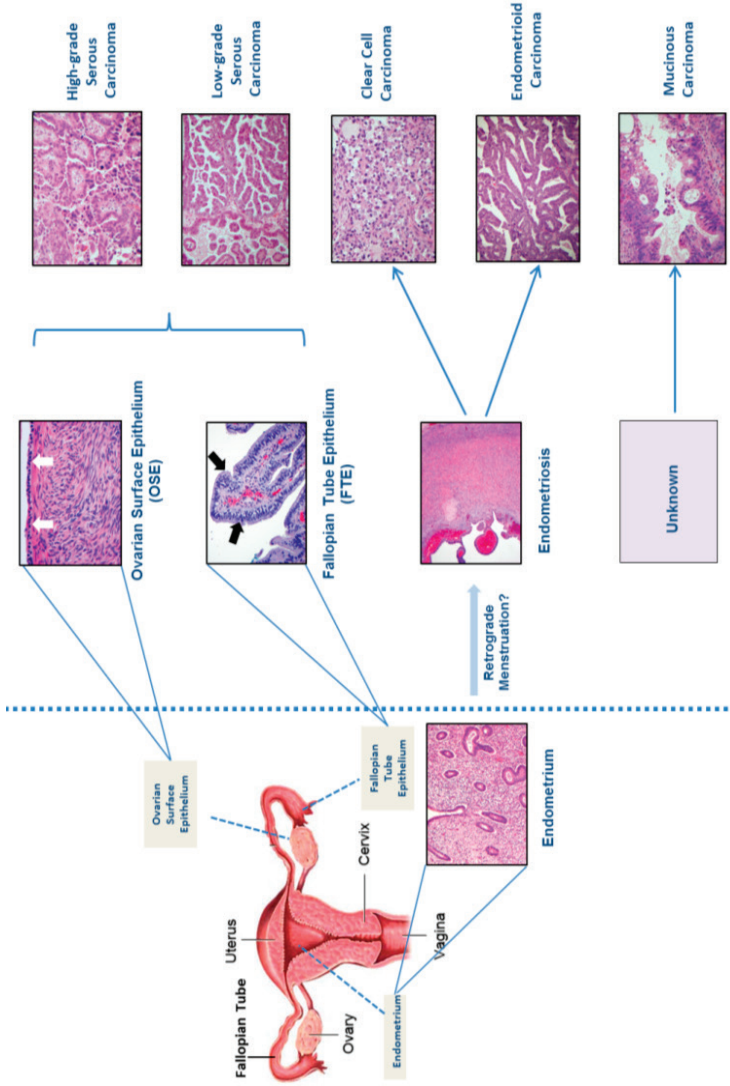

FIGURE 2-1 Potential cellular origins of ovarian carcinomas.
NOTES: Data suggest that many ovarian carcinomas may originate from outside the ovaries. However, questions still remain regarding their origins and progression. White arrows indicate OSE, black arrows indicate FTE.
SOURCE: Photographs of pathology slides reprinted with permission from Kathleen Cho (2016).

intraepithelial carcinomas (STICs), that closely resembled HGSC (Piek et al., 2001a). Subsequent studies identified STICs in about 6 to 10 percent of tubes that had been prophylactically removed from genetically predisposed women, but the studies failed to identify comparable HGSC precursor lesions in their ovaries (Callahan et al., 2007; Shaw et al., 2009). The development of a protocol in which the fimbriated end of the fallopian tube was sectioned and extensively examined (the SEE-FIM protocol) allowed for a more detailed analysis of the fallopian tube, and researchers subsequently identified STICs or small tubal HGSCs in 50 to 70 percent of women with HGSC, most of whom had advanced-stage disease (Kindelberger et al., 2007; Lee et al., 2006; Przybycin et al., 2010). STICs were also identified in women with HGSC who lacked germline *BRCA1* or *BRCA2* mutations, which indicated that these lesions can also form in women without a known hereditary mutation (Kindelberger et al., 2007). Moreover, STICs were frequently detected in the fimbria, finger-like projections at the end of the fallopian tube that are closely associated with the ovaries. Collectively, these findings suggest that many HGSCs may actually originate in fallopian tube epithelium (FTE). Cancer cells from STICs or early tubal HGSCs implanted in the ovary could give the false impression that the tumor originated in the ovary (Piek et al., 2001b, 2003). Various studies have supported a clonal relationship between STICs and concomitant HGSC by identifying identical *TP53* and other mutations (Kindelberger et al., 2007; Lee et al., 2007; McDaniel et al., 2015). Furthermore, gene expression profiling has demonstrated that HGSCs are more closely related to FTE than to OSE (Kurman and Shih, 2010; Marquez et al., 2005).

During ovulation, breaches in the OSE may allow detached tubal epithelium to implant in the ovary. Indeed, benign tubal-type epithelium is often identified in the ovary, but it remains unclear whether this ectopic tubal epithelium, known as endosalpingiosis, is actually imported to the ovary or arises from cells intrinsic to the ovary that are capable of acquiring tubal-type differentiation through a process known as metaplasia. The OSE can invaginate into the underlying ovarian stroma, forming so-called inclusion glands or cysts. Some HGSCs may arise from the OSE, from inclusion glands and cysts, from ovarian endosalpingiosis, or from other cells in the ovary without first involving the fallopian tube (Auersperg, 2013). Recent work done in a mouse model suggests that ovarian carcinomas may arise from a susceptible population of cells with stem cell–like properties that are present where the OSE, FTE, and peritoneal mesothelium converge (Flesken-Nikitin et al., 2013; Ng and Barker, 2015).

Despite a high proportion of STIC lesions being identified in women with HGSCs, questions still remain regarding HGSC origin, particularly those carcinomas that show no involvement of the fallopian tube. It will be necessary to develop additional studies and models in order to better

understand which cells undergo neoplastic transformation to HGSC and whether these are cells with stem cell–like properties. Given the remaining uncertainties regarding the origin of HGSC, the current (revised in 2014) International Federation of Gynecology and Obstetrics staging criteria for ovarian cancer combine cancers of the ovary, fallopian tube, and peritoneum into a single unified staging system (Mutch and Prat, 2014).

Sources of Other Ovarian Carcinomas

HGSC is not the only ovarian carcinoma that has been suggested to arise from nonovarian tissues. Studies indicate that endometriosis is associated with 15 to 50 percent of CCCs and ECs and that women with endometriosis are two to three times more likely to develop ovarian cancer (Brinton et al., 2005; DePriest et al., 1992; Erzen et al., 2001; Forte et al., 2014; Pavone and Lyttle, 2015; Rossing et al., 2008; Sainz de la Cuesta et al., 1996; Yoshikawa et al., 2000). The mechanisms by which endometriosis develops remain poorly understood. More than 90 years ago it was suggested that endometrial tissue might implant outside of the endometrium via retrograde menstruation (Sampson, 1927). More recently, it has been suggested that endometriosis arises from endometrial stem cells or progenitor cells that are disseminated outside the endometrium around the time of birth and then stimulated to differentiate after menarche (Brosens and Benagiano, 2015). In some cases, a transition from endometriotic cysts to EC or CCC has been observed by morphologic and molecular genetic studies (Fukunaga et al., 1997; Sainz de la Cuesta et al., 1996; Veras et al., 2009). Around 10 percent of ovarian ECs are associated with synchronous uterine ECs at the time of diagnosis (Soliman et al., 2004; Zaino et al., 2001). The shared mutational spectrum of endometriosis-associated ovarian cancers and uterine ECs suggests a common origin, likely attributable to endometriosis.

LGSCs frequently arise in association with serous borderline tumors—ovarian tumors that have some features similar to carcinomas—but they usually behave in a benign fashion. However, the origin of serous borderline tumors is unclear. Some investigators have proposed that cells from a fallopian tube lesion, termed papillary tubal hyperplasia, detach and implant in the ovary and subsequently give rise to endosalpingiosis and serous borderline tumors (Kurman et al., 2011; Robey and Silva, 1989).

Finally, the cellular origin of MCs remains unclear. Most MCs and the mucinous cystadenomas and borderline tumors from which they often arise display intestinal-type glandular differentiation and express intestinal-type protein markers (e.g., cytokeratin 20 and CDX2). The reason for this is poorly understood, particularly because intestinal differentiation is not a feature of normal epithelia in the female genital tract (e.g., organs derived

from the Müllerian ducts during embryological development). Only a small subset of MCs display the sort of endocervical-type differentiation that suggests Müllerian origin. Recent studies suggest that at least some MCs may be derived from a type of ovarian germ cell tumor known as a mature teratoma (Fujii et al., 2014; Kerr et al., 2013). Mature teratomas are ovarian germ cell tumors that are typically composed of tissues derived from two or three germ layers in the developing embryo (i.e., ectoderm, mesoderm, and endoderm). Occasionally, teratomas may display tissue from only one germ layer (the so-called monodermal teratomas). If this is the case, the least common of the major types of ovarian cancer may prove to be the only one that arises from cells intrinsic to the ovaries. Recently, it has been suggested that some mucinous tumors may arise from another type of ovarian tumor known as a Brenner tumor, based on a clonal relationship between the Brenner tumor and associated mucinous tumor components (Wang et al., 2015).

Implications

In summary, only a small fraction of ovarian carcinomas may actually originate in the ovaries, and in response to that understanding, a paradigm shift is occurring that is moving the focus away from seeing the ovaries as the source of most ovarian carcinomas (Kuhn et al., 2012). This shift in thinking has significant clinical implications. For example, the performance of prophylactic salpingectomy alone may prove to be a strategy for reducing the incidence (and mortality) of ovarian carcinomas. (See Chapter 3 for more on prophylactic salpingectomy.) Furthermore, knowing where these early precursor lesions start can help direct the development of new imaging and other techniques to detect precursor lesions before they spread to the ovaries and elsewhere.

Although more work is required to determine the origins of ovarian carcinomas definitively, it is clear that the ovaries provide a highly receptive site from which malignant cells can spread and grow (Asotra et al., 2009). This is not a new insight. The ability for cancer cells (seeds) to target specific organs (soil) has been recognized since the late 18th century, when Paget described the "seed and soil hypothesis" (Fidler, 2003; Paget, 1889). However, as will be discussed later in this chapter, evaluating these theories, developing better methods of early detection and prevention, and designing new therapies is difficult without having the proper experimental systems with which to test their validity.

THE OMICS[1] OF OVARIAN CANCERS

Advancing technologies and improved analytical methods are making it possible for researchers to explore the landscape of ovarian cancers in a variety of novel ways and, in particular, to uncover new information on the genomics, transcriptomics, epigenomics, proteomics, and metabolomics of ovarian cancers. These studies accrue large amounts of what is referred to as *omics* data, and it seems likely that the best way to analyze and study this information is to use a systems biology approach that explores the interactions of proteins, gene expression, and metabolism in order to gain useful insights into the biology of ovarian cancer (Gehlenborg et al., 2010). This section describes some of the highlights of research in ovarian cancer omics; because of the rapid development of these technologies, it was not possible to offer a completely comprehensive look at such research.

Genomics

All cancers develop as a consequence of an accumulation of genetic alterations or other molecular defects. The majority of these accumulated genetic alterations lead to abnormal cellular functions such as uncontrolled growth, angiogenesis, and immune evasion (Hanahan and Weinberg, 2011). Some cancers develop through a germline (inherited) mutation, but most advance through a series of steps that begin with somatic (acquired) mutations in the tissue of origin. Many of these mutations result in the inactivation or activation of genes known, respectively, as tumor suppressors and oncogenes. These genes encode proteins that can either inhibit (tumor suppressors) or promote (oncogenes) the growth of ovarian carcinomas. The Cancer Genome Atlas (TCGA),[2] a National Cancer Institute–supported effort to molecularly characterize various cancers, developed a catalogue of molecular abnormalities identified from a pool of 489 HGSC tumor samples. However, many research groups have been identifying other molecular abnormalities in the other ovarian carcinoma subtypes (see Table 2-1).

Inherited Mutations

A strong risk factor for ovarian cancer is having a family history of ovarian cancer. Women in families with several cases of ovarian carcinomas usually have mutations in *BRCA1* and *BRCA2*, which are good risk predictors. Together, *BRCA1* and *BRCA2* account for around 15 percent

[1] *Omics* is a term encompassing multiple molecular disciplines that involve the characterization of global sets of biological molecules such as DNAs, RNAs, proteins, and metabolites (IOM, 2012).

[2] For more information, see http://www.tcga.cancer.gov (accessed September 1, 2015).

TABLE 2-1
Characteristic Mutations in Ovarian Carcinomas

Carcinoma Subtype	Gene Activation	Gene Inactivation
HGSC	• No frequent mutations	• *BRCA1*, *BRCA2*: tumor suppressor genes that help repair DNA damage or destroy cells if DNA cannot be repaired • *TP53*: a tumor suppressor commonly mutated in cancers and crucial for genomic stability and DNA repair
LGSC	• *BRAF*: an oncogene involved with intracellular signaling involved with directing cell growth • *KRAS*: an oncogene that recruits and activates proteins necessary for tumor growth	• Unknown
MC	• *BRAF* • *ERBB2*: a receptor tyrosine kinase that can interact with signaling molecules to promote tumor growth and block cell death. It is commonly amplified or overexpressed in cancers • *KRAS*	• *CDKN2A*: a tumor suppressor that induces cell cycle arrest • *RNF43*: a tumor suppressor that inhibits WNT signaling pathway • *TP53*
EC	• *CTNNB1*: operates as a signal transducer to regulate gene transcription and cell–cell adhesion • *KRAS* • *PIK3CA*: promotes cell survival, growth, and migration • *PPP2R1A*: regulates signaling pathways that inhibit cell growth and division	• *ARID1A*: regulates gene by altering the accessibility of transcription factors to DNA • *BRCA1*, *BRCA2* • *PTEN*: a tumor suppressor that inhibits cellular growth. This gene is often mutated in cancer
CCC	• *KRAS* • *PIK3CA* • *PPP2R1A*	• *ARID1A* • *PTEN* • *TP53*

NOTE: The descriptions describe the functions of the proteins encoded by the genes listed above.

SOURCES: Anglesio et al., 2013a; Belanger et al., 2015; Cancer Genome Atlas Research Network, 2011; Della Pepa et al., 2015; Garrett et al., 2001; Gemignani et al., 2003; Jones et al., 2010; McConechy et al., 2011, 2014; Merritt and Cramer, 2010; Ryland et al., 2015; I. M. Shih et al., 2011; Zhai et al., 2015.

of all ovarian cancers (Pal et al., 2005). In one study looking at Ashkenazi Jewish women, *BRCA1* mutation carriers were found to have a 40 to 50 percent cumulative lifetime risk of ovarian cancer and *BRCA2* mutation carriers to have a 20 to 30 percent cumulative lifetime risk (King et al., 2003). *BRCA1* and *BRCA2* mutations also account for about 5 to 10 percent of all breast cancers and 20 to 25 percent of hereditary breast cancers (Campeau et al., 2008; Easton, 1999). Additional high-risk ovarian cancer susceptibility genes include *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, and *TP53*; other potential susceptibility genes continue to emerge through the use of genome-wide association studies (Kuchenbaecker et al., 2015), which have been able to identify a spectrum of susceptibility genes in ovarian tumor samples, ranging from common to rare variants (Pharoah et al., 2002). Many susceptibility genes are involved in DNA repair; mutations in such genes leave a cell unable to properly correct DNA damage, which helps explain why women with mutations in these genes have a higher risk of getting ovarian cancer in their lifetimes. Chapter 3 discusses the importance of identifying women with genetic susceptibility in order to improve prevention and early detection.

Acquired Mutations

HGSCs have frequent mutations in *TP53* and, indeed, are likely the type of solid tumor with the greatest number of *TP53* mutations, except for select inherited cancer syndromes (Belanger et al., 2015; Cancer Genome Atlas Research Network, 2011). *TP53* mutations are found in more than approximately 95 percent of HGSCs (Ahmed et al., 2010; Cancer Genome Atlas Research Network, 2011). Although most serous tumors develop as de novo high-grade lesions with early alterations of *TP53*, it is thought that in some cases the tumors stem from previously established lower-grade tumors (Dehari et al., 2007). One reanalysis of molecularly characterized *TP53* mutation-negative cases by specialty pathologists indicated that most of these cases were not truly HGSCs (Vang et al., 2015). Some of the previous genetic studies of serous carcinoma have been confounded by the inclusion of other, non-serous subtypes of ovarian carcinoma.

Somatic mutations in *BRCA1* and *BRCA2* are found to occur in almost one-third of HGSCs (Hennessy et al., 2010). A recent survey of putative homologous recombination gene mutations identified rare somatic mutations in *BRIP1*, *CHEK2*, and *RAD51C* among the advanced-stage HGSCs (Pennington et al., 2014). TCGA, which has comprehensively sequenced the exomes of more than 300 cases, not only found mutations in *TP53*, *BRCA1*, and *BRCA2*, but also identified *NF1* and *FAT3* as rare genes that were mutated in more than 3 percent of cases studied. Copy number alterations are extensive in HGSCs and spread throughout the genome, resulting

in HGSC being a very complex solid tumor. Recurrent amplifications found in *CCNE1*, *PIK3CA*, *KRAS*, and *MYC* may have prognostic or therapeutic significance (Pennington et al., 2014). Focal deletions identified in *PTEN*, *RB1*, *NF1*, and *CDKN2A* also have the potential to affect prognosis and treatment outcomes (Martins et al., 2014).

Transcriptomics

Transcriptomics is the study of all RNAs—including mRNA, microRNA (miR), long noncoding RNA, and small RNA transcripts from DNA—in a cell or tissue. Historically, the study of tumor-specific alterations to DNA represented the major focus in cancer research. It is now recognized, however, that RNA may also be a useful diagnostic and therapeutic target. The study of transcriptomics has progressed significantly in large part because RNA-sequencing has advanced to the point that it is possible to make genome-wide expression measurements. The comparison of RNA-seq data from normal and malignant tissues makes it possible to identify tumor-specific RNA. For instance, one recent analysis of mRNA in HGSC successfully identified tumor-specific mRNA (Barrett et al., 2015). Just as DNA in circulating tumor cells is being investigated as a noninvasive means to detect the presence of ovarian cancer, it is possible that RNA can serve a similar function (Kinde et al., 2013). RNA is also capable of regulating the expression of protein. For example, miR can be used to target mRNA that encodes specific genes and thus to control gene expression and biologic function by regulating mRNA turnover and translation (Eitan et al., 2009; K. K. Shih et al., 2011). Studies of ovarian cancer have noted differential expressions of miR that are associated with prognosis and platinum resistance (Eitan et al., 2009; K. K. Shih et al., 2011). Work continues to progress in this field and may eventually provide a successful avenue for tumor detection and therapy.

Epigenomics

Epigenomics is the study of reversible, inheritable modifications to DNA and chromatin that are independent of changes in DNA sequence. These modifications can alter how accessible DNA is to transcription factors and either promote or inhibit the expression of genes. The most common epigenetic modifications are DNA methylation and histone modification. Epigenetic studies in ovarian cancer identified hypermethylated genes in the hedgehog signaling pathway, which is known to promote the development of cancers and is associated with poor prognosis (Huang et al., 2013). Promoter methylation of *BRCA1* is found in approximately 10 percent of HGSC cases and is correlated with decreased gene and protein expression

(Cancer Genome Atlas Research Network, 2011; Garg et al., 2013), but the clinical significance of this *BRCA1* promoter methylation is unclear. Demethylating agents have been shown to have activity in platinum-resistant tumors (Matei et al., 2012). Treatment with demethylating agents has also been shown to have broad immune stimulatory effects and may work well in combination with immunotherapy (Li et al., 2014). MiR-mediated epigenetic regulation can also lead to changes in gene expression and cell phenotype (Mishra and Johnsen, 2014). This epigenetic regulation can allow cancer cells to better adapt to their environment, which can even promote drug resistance (Berry and Bapat, 2008). Research in this area may lead to the development of new targets and more specific ovarian cancer therapies.

Proteomics and Metabolomics

Proteomic and metabolomic profiling can provide new insights into ovarian cancer that are not apparent from genomic analysis. With the possibility of analyzing thousands of proteins, which can be simultaneously altered, comparative proteomics represents a promising model of biomarker discovery for ovarian cancer detection and monitoring (Orsini et al., 2013). Using proteomic analysis to map out signaling pathways in ovarian cancer cells analysis should make it possible to design novel drugs and to optimize the use of molecularly targeted agents against crucial biologically active pathways (Toss et al., 2013). Researchers are analyzing ovarian tumor tissue, cell lines, urine, ascites fluid, and blood samples in search of metabolites and proteins to serve as promising biomarkers (Emori and Drapkin, 2014; Toss et al., 2013). Several such markers have been identified (e.g., inter-alpha-trypsin inhibitor heavy chain H4 and transferrin), but many of them have turned out to not be specific to cancer (Ahmed et al., 2005; Zhang et al., 2004). The significance of and degree of specificity and sensitivity of these markers for ovarian cancer both remain to be explored, and to date no single test or modality has been able to provide an early diagnosis of ovarian cancer.

TUMOR HETEROGENEITY

Ovarian cancers are heterogeneous tumors that can change in various ways as the disease progresses. Only a few small studies have investigated these variations in a comprehensive manner. One recent study of 14 patients indicated that most tumors undergo clonal expansion in a metastasis-to-metastasis pattern, suggesting a continued evolution throughout anatomic dissemination rather than multiple simultaneous expansions from a common precursor clone (Schwarz et al., 2015). Furthermore, there appeared to be limited clonal expansion between primary tumor specimens and tumors

after neoadjuvant chemotherapy. However, in two cases of recurrent disease there was marked clonal expansion from a subclone that was present at diagnosis (Schwarz et al., 2015). Array comparative-genomics hybridization studies have found low copy-number variations between pre- and post-neoadjuvant chemotherapy specimens, suggesting that a dominant clone is present at diagnosis (Cooke et al., 2010).

Regarding mutational burdens, a study of six patients found that approximately 50 percent of mutations were shared through disease progression, with *TP53* mutations being the only genetic mutation found in all specimens—a state of affairs that reflects *TP53*'s early role in tumorigenesis (Bashashati et al., 2013). Both copy-number alterations and mutations were highly heterogeneous and independent of one another. The phylogenic evolution of each of the tumors was unique and complex, reflecting the varied mechanisms of drug resistance. Pre- and post-treatment magnetic resonance imaging parameters have also been shown to vary by anatomic site, with more changes in the ovary than in metastatic deposits, and these measurements correspond with treatment response (Sala et al., 2012). Taken together, the limited studies to date demonstrate that HGSCs are molecularly diverse and continually evolving and have broad subclonal structure. An improved understanding of clonal diversity and tumor heterogeneity is needed.

ADAPTATION AND DRUG RESISTANCE

Both acquired and de novo chemoresistance remain a significant clinical challenge in ovarian cancer (discussed further in Chapter 4). The biological underpinnings of resistance are not well understood. Identifying the genes involved in responding to chemotherapy and survival may contribute to a better understanding of prognosis and potentially guide the selection of treatment options to help circumvent chemoresistance. Drug resistance, especially platinum resistance, is not limited to ovarian cancer, and there is much still to learn regarding drug resistance in all cancers. However, most cancers other than ovarian cancer have a variety of treatment options available to overcome resistance when a specific therapeutic is no longer effective. Ovarian cancer is hindered by the lack of additional therapeutic options, and therefore an improved understanding of the molecular mechanisms underlying drug resistance in ovarian carcinomas could be useful for devising new targeted therapeutic approaches to overcome or bypass resistance.

To date, several mechanisms have been proposed to explain the development of chemoresistance. Recent genetic analyses suggest that resistant clones may be present in small populations at diagnosis and then undergo selection in the face of chemotherapy. Alternatively, adaptive responses

may exist that induce resistance mechanisms during active chemotherapy treatment (Cunnea and Stronach, 2014). Other mechanisms that have been well established include reversion mutations in *BRCA1* or *BRCA2* that restore homologous recombination DNA repair and decrease sensitivity to platinum and other chemotherapeutic agents (Edwards et al., 2008; Sakai et al., 2008). Targeting the drivers of *BRCA1* and *BRCA2* expression is one possible approach to inducing homologous recombination deficiency in tumors with intact *BRCA1* and *BRCA2* function. Potential therapeutic targets include the E26 transformation-specific family of transcription factors, the retinoblastoma tumor suppressor (RB) pathway, and other regulators of the DNA damage response (Wiedemeyer et al., 2014). *CCNE1* is overexpressed in about 20 percent of HGSC tumors and appears to upregulate members of the *BRCA*/homologous recombination damage-repair complex (Etemadmoghadam et al., 2013). Therefore, the inhibition of the proteasome and homologous recombination is one potential approach to overcoming the platinum resistance seen in *CCNE1*-amplified tumors.

Among the mechanisms that have already been employed to overcome platinum resistance are dose-dense chemotherapy and varying dose intensity. Dose-dense treatment is often applied by giving paclitaxel on a weekly, rather than 3-weekly, schedule. This approach may have effects on growth kinetics, log-kill, and neovascularization (Pinato et al., 2013). Another potential approach to overcoming platinum resistance is using targeted inhibitors to regulate signaling pathways that affect various mechanisms, including drug uptake, efflux, and binding. The use of different drugs with non-overlapping mechanisms of action may also be an important approach to overcoming platinum and other types of drug resistance.

TUMOR MICROENVIRONMENT

Cancers form because of a series of mutations in oncogenes or tumor suppressor genes, but the specific tumor microenvironment can shape the transcriptional and functional diversity of the resulting cancer cells (Abelson et al., 2013; Cancer Genome Atlas Research Network, 2011; Hanahan and Weinberg, 2011; Myers et al., 2006; Schwarz et al., 2015; Tlsty and Coussens, 2006; Touboul et al., 2014). Ovarian tumor cells exist in a complex, dynamic, and multifaceted microenvironment that includes blood vessels (e.g., endothelial cells) and lymphatic networks, immune cells (e.g., infiltrating myeloid- and lymphoid-lineage cells), mesenchymal stem cells, extracellular matrix (e.g., fibroblasts, collagen, and proteoglycans), and connective tissue (e.g., adipose cells) (Hanahan and Coussens, 2012; Kenny et al., 2007; Quail and Joyce, 2013; Tlsty and Coussens, 2006). Analyses of the sequence of histologic changes that occur between tumor cells and the surrounding stromal tissues demonstrate the importance of

the tumor microenvironment (Hanahan and Weinberg, 2011). In addition, clonally expanded cell lines from single ovarian cancer cells demonstrate a phenotypic heterogeneity (plasticity) within the individual tumors with the capacity to restore self-renewal markers that are dependent on the tumor microenvironment (Abelson et al., 2013).

The Role of the Tumor Microenvironment in Ovarian Cancers

The microenvironment plays a key role in a number of stages of cancer progression, including local evasion from immune surveillance, sustained growth, invasion, and metastasis (Chen et al., 2015). Tumor and host cells physically interact and also secrete cytokines, chemokines, growth factors, and proteases that cleave and modify the structure of the extracellular matrix. Infiltrating immune cells, cancer-associated fibroblastic cells, and angiogenic vascular cells all contribute to the ability of cancer cells to keep proliferating, evade growth suppressors, avoid immune destruction, activate invasion and metastasis, induce angiogenesis, and resist cell death (Hanahan and Coussens, 2012). For example, myeloid-derived suppressor cells are mobilized during tumorigenesis and infiltrate tumors in order to promote vascularization and disrupt immune surveillance (Quail and Joyce, 2013). Infiltrating immune cells can also bind directly to cancer cells in order to suppress the activation of cell death pathways. Furthermore, activated macrophages that secrete proteases are recruited to the neoplastic site (Hanahan and Weinberg, 2011; Junttila and de Sauvage, 2013; Mroue and Bissell, 2013).

Cancer cells and stromal cells also stimulate angiogenesis. Angiogenic vascular cells not only attenuate cell death by the vascularization of tumors, they also secrete growth-promoting trophic factors as well as inhibitors of cell death (Butler et al., 2010; Castells et al., 2013). Although heterotypic signaling through paracrine signaling loops of cytokines or growth factors and their receptors is a key means of intercellular communication within the tumor microenvironment, exosome shedding from both tumor and stromal cells has recently been suggested as another possible mode of cell–cell signaling in the tumor microenvironment (Barcellos-Hoff et al., 2013). Thus, the interactions between the tumor and the stromal cells accelerate disease progression by eliciting effects on the cellular growth and metabolism of both neoplastic and stromal cell types.

The Role of the Immune System in Ovarian Cancers

Cancer cells evade immunological elimination by inducing the expression of T cell inhibitory receptors on tumor cells and immune cells and by recruiting immunosuppressive cells such as regulatory T cells and tumor-

associated macrophages (Wefers et al., 2015). The presence of macrophages correlates with malignancy in both serous and mucinous ovarian carcinomas (Hagemann et al., 2006; Kawamura et al., 2009; Takaishi et al., 2010). Tumor-associated macrophages turn into immunosuppressive cells as the tumor progresses (Hagemann et al., 2006; Mantovani and Sica, 2010). The macrophages continue to recruit regulatory T cells, which further potentiates the suppressive activity of the macrophages through cytokine production (Wefers et al., 2015). Macrophage proteases also remodel the extracellular matrix, resulting in the disruption of tissue architecture, which in turn allows cancer cells to escape the constraints imposed by the microenvironment (Balkwill et al., 2005; Karin and Greten, 2005). The degraded extracellular matrix possesses fragments thought to exert potent effects on processes such as angiogenesis (Folkman, 2006). Angiogenesis is essential for supplying blood and oxygen. Conversely, inadequate vascular function can result in hypoxia around tumor vessels, which contributes to metastasis by regulating the expression of genes through hypoxia-inducible transcription factors that alter vascular integrity (Kashiwagi et al., 2005).

Mechanisms of Metastasis

The pelvic area provides a unique environment for ovarian cancer cells to grow and metastasize. Many of the organs in the pelvic region are in close proximity and lack the physical barriers among them that could hinder the spread of cancer. The epithelial–mesenchymal transition of cancer cells is an important step in tumor metastasis. Recent data indicate that proteins that regulate actin cross-linking and coordinate the assembly of cell junctions may be critical regulators of this transition (Zhu et al., 2015).

Peritoneal recurrences of ovarian cancer indicate that a niche exists where cells are protected. Diverse stromal cell types that enhance ectopic cell survival by stimulating cells to exit dormancy also infiltrate metastatic lesions (Catena et al., 2013; Granot et al., 2011; Quail and Joyce, 2013; Tlsty and Coussens, 2006). For example, metastatic ovarian carcinomas typically seed into the adipose tissue of the peritoneum, which results in the reprogramming of adipocytes to generate free fatty acids that are then used by the cancer cells to generate ATP. This protects the cancer cells from apoptotic cell death, thereby enhancing their colonization (Nieman et al., 2011). The metastatic cells continue to acquire genetic changes that can lead toward more aggressive clones (Cancer Genome Atlas Research Network, 2011; Myers et al., 2006).

Cancer stem cells are able to produce primary and recurrent disease (Ffrench et al., 2014). One of the properties of cancer stem cells is self-renewal, which underlies tumorigenesis and differentiation and contributes

to the heterogeneity of cancer cells. Cancer stem cells have been identified in ovarian cancers. These cells may mediate tumor metastasis and, by virtue of their relative resistance to chemotherapy and radiotherapy, may contribute to the treatment resistance commonly seen in ovarian cancers (Zhang et al., 2008). Cancer stem cells are typically resistant to chemotherapy because of their decreased oxidative stress response, increased genomic stability, and expression of multiple drug resistance transporters, and they are therefore a source for tumor relapse (Visvader and Lindeman, 2008). Cancer stem cells are believed to spread by direct surface contact as well as by migration to distant areas following the flow of peritoneal fluids (Ffrench et al., 2014). Furthermore, the successful seeding of cancer stem cells at secondary sites can occur when cells breach the endothelial basement membrane (Bissell and Hines, 2011). Using anatomically joined mice, Sood and colleagues demonstrated the metastasis of ovarian cancer cells through the blood circulation (Pradeep et al., 2014).

Abnormal regulation of miR expression has been documented in ovarian cancers (Miles et al., 2012). One study identified and characterized a microenvironment-induced downregulation of miR-193b in metastasizing ovarian cancer cells (Mitra et al., 2015). The reduction in miR-193b resulted in an increased expression of its target urokinase-type plasminogen activator, a known tumor-associated protease. These changes correlated with the invasion and proliferation of the cancer cells. Another study showed that a copy number gain of miR-569 led to a loss of *TP53INP1*, which contributed to the proliferation and survival of ovarian epithelial cancer cells (Chaluvally-Raghavan et al., 2014). A small number of long noncoding RNAs have also been associated with ovarian cancer (Ren et al., 2015). However, it is not clear whether these long noncoding RNAs have a function in the cancer phenotype or what their mechanism of action is.

Mesenchymal stem cells are multipotent adherent cells that incorporate into the stroma of solid tumors (Karnoub et al., 2007; Klopp et al., 2007; Studeny et al., 2004). These cells contribute to the proliferation, chemoresistance, infiltration, and metastasis of ovarian cancer cells (Bianco et al., 2008), and they are able to mobilize in the circulation of ovarian cancer patients (Roodhart et al., 2008). Mesenchymal stem cells also have an immunosuppressive effect on T lymphocytes, inhibit apoptosis, stimulate angiogenesis, recruit and regulate the proliferation of cancer stem cells, and attenuate oxidative stress (Le Blanc and Ringden, 2007; Strioga et al., 2012). Cytokine secretion by ovarian cancer cells results in the mesenchymal stem cell infiltration of the tumor stromal environment (Wels et al., 2008). Expression profiles change with an increase in secretion of paracrine factors that stimulates motility and metastatic abilities of tumor cells as well as pro-angiogenic molecules (Karnoub et al., 2007). In vitro co-culture

experiments have shown that mesenchymal stem cells trigger expression differences in ovarian cancer cells, leading to metastatic characteristics such as adherence, invasion, and migration (Lis et al., 2012).

DEVELOPMENT OF EXPERIMENTAL MODEL SYSTEMS

Because of the extreme heterogeneity of ovarian cancers, it is difficult to design a single system to replicate the myriad human manifestations of the disease. Furthermore, many experimental models may not accurately represent the disease pathogenesis (e.g., assuming origination in the ovaries). However, research efforts have led to the development of a number of newer in vitro and in vivo models that may assist in the development of new strategies for the prevention, early detection, and treatment of ovarian cancers.

Cell Culture Models

Cancer cell lines are the most commonly used models in cancer research, and their use has advanced the understanding of cancer biology. However, because of the heterogeneity and the distinct molecular features of different ovarian carcinomas, not all ovarian cancer cell lines are representative of all ovarian cancers (see Table 2-2). One study analyzed a panel of commonly used ovarian cancer cell lines and found significant genetic differences between them and HGSC tumor samples from women (Domcke et al., 2013). Furthermore, the genetics of several rarely used cell lines were found to more closely resemble the genetics of the primary tumors than of some of the more commonly used cell lines found in the literature. Another study found that several commonly used cell lines were incorrectly classified with respect to their tumor subtype (Anglesio et al., 2013b). Because cancer cell lines are often used to identify and test new biomarkers and drug targets, cell lines need to be properly validated (IOM, 2012). Recently, a collection of 25 rigorously validated ovarian cancer cell lines was reported to represent the tumor types from which they are derived (Ince et al., 2015).

Researchers study ovarian cancer by growing cancer cells obtained from ovarian cancer patients in culture dishes. Cancer cells are typically grown in a single layer and spread across the cell culture dish. However, newer three-dimensional cell culture systems are becoming more widely used because researchers can introduce various components (e.g., adipocytes, immune cells, and endothelial cells) in order to reconstruct the tumor microenvironment (White et al., 2014). Three-dimensional culture systems also produce a histologic morphology reminiscent of the tumor from which they are derived. In addition, as compared with monolayer cell cultures, three-dimensional culture systems more accurately depict cell prolifera-

TABLE 2-2
Representative Ovarian Carcinoma Cell Lines

Histologic Subtype	Molecular Features	Cell Lines
HGSC	Near universal somatic *TP53* mutations, high-frequency *BRCA1* and *BRCA2* alterations, extensive genomic instability, common *MYC* and *CCNE1* amplifications	CAOV3*, CAOV4*, COV318*, COV362*, COV504*, JHOS2, JHOS4, Kuramochi*, OAW28*, OVCAR3*, OVCAR4*, OVCAR5, OVKATE, OVSAHO, PEA1, PEA2, PEO1, PEO4, PEO14, PEO23, SNU119
EC	Few *TP53*, *BRCA1*, *BRCA2* mutations, frequent *ARID1A* mutations, common *PTEN*, *PIK3CA*, and *CTNNB1* mutations or loss	A2780*, SKOV3*, TOV112D*
CCC	Few *TP53*, *BRCA1*, *BRCA2* mutations, frequent *ARID1A*, *PIK3CA*, and *PTEN* mutations or loss, high expression of *HNF1B*	2008, JHOC-5, JHOC-7, JHOC-9, OVMANA*, OVTOKO*, RMG-2
MC	Some *TP53* mutations, few *BRCA1*, *BRCA2* mutations, frequent *KRAS* mutations, some *ERBB2* amplification	COV644, MCAS*
Other	Mixed features of more than one subtype, features precluding classification, or conflicting classification by referenced sources	ES2*, IGROV1*, OV90*, OVCAR8*, TOV21G*

NOTE: Asterisk indicates classification supported by more than one reference.

SOURCES: Anglesio et al., 2013b; Beaufort et al., 2014; Domcke et al., 2013; Ince et al., 2015.

tion, drug response, phenotypic heterogeneity, and changes in gene expression and cell behavior. A human fallopian tube co-culture system of both secretory and ciliated cells was developed from primary human surgical specimens (Fotheringham et al., 2011; Levanon et al., 2010). This model mimics the properties of tubal epithelium in situ, including morphological and immune-phenotypic properties. A similar model was developed using oviduct epithelium (equivalent to human FTE) from pigs (Miessen et al., 2011). Recently, even more complex in vitro model systems called human tissue chips have been developed (Benam et al., 2015). These models incorporate the tissue structure and physiology to provide a more accurate setting in order to better evaluate new therapies and disease mechanisms. These robust models more accurately represent the human disease. However, more models are needed to incorporate other important factors in ovarian cancer, such as the endocrine system.

Animal Models[3]

Genetically engineered mouse models (GEMMs) that replicate the morphological and biological features of a particular histologic type of ovarian cancer are useful for studying tumor biology and for the preclinical testing of new strategies for prevention, early detection, and treatment of ovarian cancer. A number of GEMMs developed over the past several years are outlined in Table 2-3; no GEMM of mucinous ovarian carcinoma has yet been reported.

Developing an ovarian cancer GEMM requires being able to modify the genes of interest in the cells of interest. The genes of interest are usually selected because they are characteristically mutated in a particular subtype of ovarian cancer (e.g., activating mutations of *Pik3ca* in ECs or CCCs, and inactivating mutations of *Trp53* and *Brca1* and *Brca2* in HGSCs). Cells of interest include OSE and FTE.

Historically, two general approaches have been used to modify the genes of interest in the development of ovarian cancer GEMMs: (1) the expression of viral proteins (e.g., SV40 Large T-Antigen) to inactivate certain tumor suppressor proteins through direct protein–protein interactions, and (2) Cre-lox technology, in which the genes of interest are engineered to carry recognition sequences (loxP sites) for a bacteriophage enzyme called Cre-recombinase (Cre). When Cre is expressed in the desired cells, Cre-mediated recombination (i.e., the excision of DNA between two loxP sites) results in the inactivation of specific tumor-suppressor genes or the activation of specific oncogenes. Some model systems are further modified in ways that allow investigators to control the timing as well as the location of Cre expression. A third approach involves infecting *p53*-deficient mouse OSE cells engineered to express the avian receptor TVA with retroviruses that express various oncogenes (Orsulic et al., 2002; Xing and Orsulic, 2005, 2006).

Most of the early ovarian cancer GEMMs were based on transforming the OSE using recombinant adenovirus to express Cre-recombinase in OSE harboring engineered tumor suppressor gene and oncogene alleles. Some of these models may also inadvertently target the FTE. However, because of the new focus on the FTE as the cell of origin of many HGSCs, some of the more recent GEMMs are based on transforming the mouse oviductal epithelium (equivalent to human FTE) using the promoters of genes expressed in the FTE to drive Cre-mediated recombination of engineered tumor suppressor and oncogene alleles. Although the oviductal models of HGSC represent a significant advance, some shortcomings remain. For example, the

[3]Gene symbols for mice are italicized, with only the first letter in uppercase and the remaining letters in lowercase to differentiate from human genes.

Pax8 promoter drives Cre expression in other Müllerian epithelia besides the FTE (e.g., endometrium), and *Ovgp1*-driven expression of SV40 T-Ag does not mimic the actual genetic alterations known to play a role in HGSC pathogenesis. Furthermore, it is not clear whether any of the models faithfully reproduce the earliest events in ovarian tumorigenesis, as all of them rely on a simultaneous mutation of more than one tumor suppressor gene or oncogene, which is unlikely in humans.

While GEMMs provide a good system to examine gene functions and disease progression, patient-derived xenografts (PDXs) provide a good model system to test drug efficacy (Hasan et al., 2015). PDXs are able to recapitulate aspects of tumors found in women because they are directly transferred from the patient into the mouse. This allows the tumor in the mouse to have properties and cell proportions that are similar to those of the original tumor (Monsma et al., 2012). Therefore, PDX mice are clearly useful for clinical and co-clinical trials because they allow drugs to be tested based on a patient's specific tumor type.

The adult laying hen is also recognized as a relevant model for human ovarian cancer, because ovarian tumors arise spontaneously in approximately 40 percent of hens around 4 years of age (King and Burdette, 2011). Ovarian tumors in hens can exhibit serous, endometrioid, mucinous, and clear cell histopathological features and express genes similar to those observed in human and mouse carcinomas including CA125; they can harbor *TP53* mutations; and they can overexpress the epidermal growth factor receptor. Ovarian cancer in hens metastasizes to similar tissues with an accumulation of ascites fluid, as occurs in humans. Because of the spontaneous formation and heterogeneity of the ovarian cancers, hens provide another model system with which to study the progression of ovarian cancer and to test novel drugs in vivo for treating it.

KEY FINDINGS AND CONCLUSIONS

The heterogeneity of ovarian cancers presents unique challenges to studying and treating ovarian cancer. The committee offers the following findings and conclusions:

- Ovarian cancer is not a single disease, and better diagnostic criteria, nomenclature, and classification are needed to standardize research and treatment.
- More research is needed to determine the sites of origin and the pathogenesis of each subtype because current evidence suggests that only a fraction of ovarian carcinomas originate in the ovaries.
- More research is needed to better understand the multitude of genetic alterations that characterize ovarian cancers in order to help

TABLE 2-3
Genetically Engineered Mouse Models

Altered Genes[a]	Delivery Method	Targeted Cell Population(s)	Comments	References
HIGH-GRADE SEROUS CARCINOMA MODELS				
Brca1; Brca2; Trp53; Pten	*Pax8*	FTE and endometrium	Mice also develop endometrial hyperplasia and adenocarcinoma	Perets et al., 2013
Brca1; Brca2; Trp53, Rb^{T121}	AdCre into bursa	OSE	*TgK18GT*$_{121}$ mice allow Cre-mediated expression of the N-terminal domain of SV40 TAg in the OSE to interfere with all three Rb pocket proteins (pRB, p107, and p130)	Szabova et al., 2012
Pten; Dicer ± ***Trp53***	*MISIIR(Amhr2)-Cre*	FTE and OSE	Tumors with *Pten* and *Dicer* inactivation initiate in fallopian tube stroma. Tumors with *Pten*, *Dicer*, and *Trp53* inactivation form tumors in tube and ovary (ovary tumors form even if tubes are removed)	Kim et al., 2012, 2015
Pten; Pik3ca^{H1047R}	AdCre into bursa	OSE	Mice also form granulosa tumors	Kinross et al., 2012
SV40 T-Antigen	AdCre into bursa	OSE	*TgCAG-LS-Tag* allows Cre-mediated expression of SV40 Tag in the OSE. *CAG* is the CMV early enhancer/chicken β-actin promoter. Tumors are very poorly differentiated; treatment with estradiol decreased survival time and induced papillary architecture	Laviolette et al., 2010
SV40 T-Antigen	*MISIIR(Amhr2)-TAg*	OSE	Female mice expressing the transgene are infertile; a subset of male transgenic mice develop Sertoli tumors	Connolly et al., 2003
Trp53; Rb1	AdCre into bursa	OSE	Other groups who used a similar approach to inactivate *Trp53* and *Brca1* (Quinn et al., 2009) or *Trp53*, *Rb1* and *Brca1* (Clark-Knowles et al., 2009) found that mice develop leiomyosarcomas rather than HGSCs	Flesken-Nikitin et al., 2003, 2013
SV40 T-Antigen	*Ovgp1-TAg*	FTE	The tumor phenotype in this model is described in greater detail by Sherman-Baust et al. (2014)	Miyoshi et al., 2002; Sherman-Baust et al., 2014

Altered Genes[a]	Delivery Method	Targeted Cell Population(s)	Comments	References
LOW-GRADE SEROUS CARCINOMA MODELS				
Pten; Kras^{G12D}	*MISIIR(Amhr2)-Cre*	OSE		Fan et al., 2009
Pten; Kras^{G12D}	*MISIIR(Amhr2)-Cre*	OSE		Mullany et al., 2011
ENDOMETRIOID CARCINOMA MODELS				
Pten; Arid1a	AdCre into bursa	OSE	Endometrioid and/or undifferentiated carcinomas arise in ~60 percent of mice within 6 months and in ~80 percent of mice within 8–9 months	Guan et al., 2014
Pten; Apc ± ***Pik3ca***^{E545K} **or** ***Trp53***	AdCre into bursa	OSE	Tumor phenotype is more aggressive with mutant *Pik3ca* or *Trp53*	Wu et al., 2013
Pten; Apc ± ***Arid1a***	AdCre into bursa	OSE	Tumor phenotype is less aggressive and tumors display more epithelial differentiation with *Arid1a* loss	Zhai et al., 2015
Pten; Ctnnb1$^{\Delta ex3}$	*MISIIR(Amhr2)-Cre*	OSE	Tumors are poorly differentiated	Tanwar et al., 2011
Pten; Apc	AdCre into bursa	OSE	Tumors are poorly differentiated with prominent spindle component	Wu et al., 2007
Pten; Kras^{G12D}	AdCre into bursa	OSE	*Kras* activation alone induces endometriosis	Dinulescu et al., 2005
CLEAR CELL CARCINOMA MODELS				
Pik3ca^{H1047R}***; Arid1a***	AdCre into bursa	OSE	Activation of *Pik3ca* results in OSE hyperplasia; *Pik3ca* activation and *Arid1a* inactivation results in CCC	Chandler et al., 2015

[a]Gene symbols for mice are italicized, with only the first letter in uppercase and the remaining letters in lowercase to differentiate from human genes.

identify and prioritize promising candidates to develop for screening, prevention, and treatment methods.

- Because many ovarian cancers become drug resistant, further biological investigations are required to explore the mechanisms of drug resistance and to identify new drug targets.
- Because of the interplay between the tumor microenvironment and ovarian tumor cells, it will be important to develop treatment strategies that extend beyond targeting the tumor cell itself, with attention being placed on components within the tumor microenvironment (e.g., immune therapy and angiogenesis inhibitors).
- New cancer research models for preclinical studies need to take into account the variability among the ovarian cancer subtypes, the heterogeneity within ovarian cancer subtypes, and the different origins of these subtypes.

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3

Prevention and Early Detection

Improving the prevention and early detection of ovarian carcinomas will be a critical component of reducing morbidity and mortality from ovarian cancer. This chapter discusses the genetic and nongenetic risk factors of the disease along with potential prevention strategies and methods for early detection and screening of ovarian cancer. In particular, this chapter identifies a number of gaps in knowledge related to identifying those women who are at highest risk for developing ovarian carcinomas, and it describes several challenges to developing screening tests for high-risk women, their families, and the general population. The chapter also explains how gaps in knowledge about the basic biology of ovarian carcinomas (as discussed in Chapter 2) hinder the development of better methods to prevent ovarian carcinomas or detect them at the earliest stage of disease progression.

RISK ASSESSMENT FOR OVARIAN CANCER

Although scientists' understanding about the early carcinogenic events of ovarian cancer is incomplete (see Chapter 2), researchers have identified several factors associated with either an increased or a decreased risk of developing ovarian cancer (see Table 3-1). While some of these risks factors cannot be modified (e.g., age and ancestry), a number of others (e.g., hormone use and diet) can be altered through lifestyle changes, pharmacological interventions, or surgery. A critical drawback, however, is that nearly all of the identified risk factors are associated predominantly with the less common and less lethal ovarian cancer subtypes and not with the most common and lethal type—high-grade serous carcinoma (HGSC). Ovarian

TABLE 3-1
Risk Factors for Ovarian Cancer

Increased Risk	Decreased Risk
Age	Oral contraceptive (OC) use
Family history of cancer	Oophorectomy
Hereditary cancer syndromes	Hysterectomy
Obesity	Tubal ligation
Nulliparity	Lactation
Hormone replacement therapy	Salpingectomy
Increased numbers of lifetime ovulatory cycles	Bilateral salpingo-oophorectomy (BSO)

SOURCE: Adapted from Permuth-Wey et al., 2014.

cancer risk factors can also vary by histologic subtype, and thus a given risk factor may increase risk for one subtype while decreasing risk for another.

Age, Race, and Ethnicity

In general, cancer risk increases with age, in part because of the natural accumulation of genetic alterations and long-term exposure to environmental factors. As noted in Chapter 1, ovarian cancer incidence also increases with age, and the age-adjusted incidence rate for women ages 65 and older is more than five times the incidence rate for women younger than age 65 (Howlader et al., 2015). Race and ethnicity have variable associations with ovarian cancer (see Chapter 1 for more on the role of race and ethnicity in ovarian cancer demographics).

Inherited Genetic Risk

A family history of ovarian cancer has a strong association with risk for ovarian cancer, and having a large number of first-degree biological relatives with an ovarian carcinoma increases a woman's risk (Jervis et al., 2014; Soegaard et al., 2009; Stratton et al., 1998; Werness and Eltabbakh, 2001). As a result, specific germline (inherited) genetic mutations are among the most well-established risk factors associated with ovarian cancer (Shulman and Dungan, 2010). Many women with a family history of cancer have a hereditary cancer syndrome (Garber and Offit, 2005). Table 3-2 describes some common genetic mutations and hereditary cancer syndromes that are found among women with ovarian cancer. Inherited genetic mutations are associated with approximately 5 to 15 percent of all ovarian carcino-

TABLE 3-2
Examples of High-Risk Ovarian Cancer Susceptibility Genes and Cancer Syndromes

Mutated Gene(s)	Cancer Syndrome
BRCA1, *BRCA2*	Hereditary breast and ovarian cancer (HBOC) syndrome
MLH1, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Lynch syndrome
TP53	Li–Fraumeni syndrome
STK11/LKB1	Peutz–Jeghers syndrome, sex cord and mucinous tumors

NOTE: Lynch syndrome is also known as hereditary nonpolyposis colorectal cancer.
SOURCES: Hampel et al., 2015; Hendriks et al., 2006; Kempers et al., 2011; Lu and Daniels, 2013; Shulman, 2010.

mas, though their distribution varies by subtype (Lynch et al., 2009). In some studies, inherited mutations have been found in up to 25 percent of women with HGSC, but up to half of these women did not have a family history of breast or ovarian cancer (Schrader et al., 2012; Walsh et al., 2011).

High- and Moderate-Risk Gene Mutations

BRCA1 and *BRCA2* are the most recognizable of the genes that increase the risk of ovarian cancer. These genes were identified in the mid-1990s as breast and ovarian cancer–risk genes, and in recent years the effect that the *BRCA1* and *BRCA2* mutations have on the risk of breast and ovarian cancers has been established (Miki et al., 1994; Rebbeck et al., 2015; Wooster et al., 1994). Germline mutations in these genes are present in approximately 10 to 15 percent of all women diagnosed with invasive ovarian carcinomas and in approximately 15 to 23 percent of women diagnosed with HGSC (Alsop et al., 2012; Pal et al., 2005; Risch et al., 2006; Zhang et al., 2011). Recently discovered single-nucleotide polymorphisms (SNPs) in other genes appear to have a role in modulating the risk of ovarian cancer in those women who have an inherited *BRCA1* or *BRCA2* mutation (Ramus et al., 2011, 2012).

Lynch syndrome is caused by deleterious mutations in DNA mismatch repair genes (see Table 3-2). The lifetime risk of ovarian cancer associated with Lynch syndrome mutations is around 8 percent, with the greatest risks associated with *MLH1* or *MSH2* (Lu and Daniels, 2013). Many of the genes in Table 3-2 are typically included in the multiplex gene panels currently offered by commercial laboratories, and National Comprehensive Cancer Network (NCCN) guidelines suggest various interventions when a woman has one or more of these genes. For example, NCCN recommends

risk-reducing surgeries (e.g., bilateral salpingo-oophorectomy) for women with mutations in *BRCA1*, *BRCA2*, and genes associated with Lynch syndrome (NCCN, 2015). Risk-reducing surgeries are discussed later in this chapter. Other moderate-risk cancer susceptibility genes often included in the panels are *CHEK2*, *PALB2*, *RAD51* family, *BRIP1*, and *BARD1* (Walsh et al., 2011). *RAD51C* and *RAD51D* mutations appear to confer a lifetime risk of 10 to 15 percent for ovarian cancer (Lancaster et al., 2015).

Advances in DNA-sequencing technologies have dramatically reduced the cost of genetic testing, and in 2013 the U.S. Supreme Court ruled that, with few exceptions, patents on naturally isolated DNA sequences are invalid.[1] The confluence of these events led to the rapid development and release of genetic tests that sequence multiple genes simultaneously—the so-called multiplex gene panels—and to the possibility of performing whole-genome sequencing (Rahman, 2014; Robson et al., 2015). With multiplex gene panels it may be possible to identify more individuals with hereditary cancer gene mutations than with testing for *BRCA1* and *BRCA2* alone (Desmond et al., 2015). However, the ability to find more mutations does not necessarily lead to a better understanding of disease risk, as little is known about the clinical impacts of a large fraction of these variants or mutations. In these cases where the clinical implications are unknown, the mutations are referred to as "variants of unknown significance" (Domchek and Nathanson, 2014; Eccles et al., 2015).

Recently, the American Society of Clinical Oncology (ASCO) recognized that for women with a personal or family history of cancer, multigene testing may be an efficient way to evaluate multiple high-penetrance genes of established clinical utility (Robson et al., 2015). ASCO further stated that providers with expertise in cancer risk assessment need to be involved in ordering and interpreting multigene panels when genes of uncertain clinical utility are included and that patients must give informed consent and be provided with pretest counseling prior to any genetic testing. ASCO also commented on the specific components that should be included in multigene panel testing.

Technological and legislative advances have combined to make genetic testing for *BRCA1* and *BRCA2* mutations much more accessible. The Patient Protection and Affordable Care Act[2] requires health plans beginning on or after September 23, 2010, to cover genetic counseling and testing for *BRCA1* and *BRCA2* mutations in women whose family history indicates a high risk for cancer. The law does not specifically cover testing using multiplex gene panels or genome-wide sequencing, and testing is not required to be covered for women whose family history does not indicate an increased

[1] *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___ (2013).

[2] Patient Protection and Affordable Care Act, Public Law 148, 111th Cong., 2nd sess. (March 23, 2010).

risk (Nelson et al., 2005, 2014). Two testing issues that the act leaves unaddressed are that *BRCA1* and *BRCA2* mutations alone do not fully account for genetic risk and that many women with inherited cancer-predisposing mutations do not have a strong family history of breast or ovarian cancer (Jervis et al., 2014; Schrader et al., 2012; Walsh et al., 2011).

Women who test positive for germline genetic mutations associated with greatly increased risk for developing ovarian cancer may benefit from enhanced screening, risk-reducing prophylactic surgery, or chemoprevention. For instance, women with a known *BRCA1* or *BRCA2* mutation who have prophylactic bilateral salpingo-oophorectomy (BSO) can reduce their risk of ovarian cancer by more than 90 percent (and, for premenopausal women, can reduce their risk for breast cancer by 50 percent) (Domchek et al., 2010).

Low-Penetrance Alleles

Genome-wide association studies have identified some common low-penetrance alleles (genes associated with a low risk) that can also contribute to the familial risk associated with ovarian cancer (Song et al., 2014). Studies using consortia have identified as many as 17 low-penetrance SNP alleles associated with ovarian cancer risk (Bojesen et al., 2013; Bolton et al., 2010; Goode et al., 2010; Kuchenbaecker et al., 2015; Permuth-Wey et al., 2013; Pharoah et al., 2013; Song et al., 2009). In general, most of the risk alleles have been more strongly associated with serous tumors, but these associations may reflect the fact that there are relatively many cases of such tumors, making it easier to find risk alleles associated with them. Using consortia increases the number of cases available for study, which may lead to more associations being uncovered, especially for the less common subtypes. For example, one study of mucinous carcinomas using consortia identified several risk alleles that had not been identified in previous studies that included multiple histologic subtypes (Kelemen et al., 2015).

Genetic Testing Guidelines and Recommendations

Cancer genetic consultation services can provide an evaluation of personal and family history for possible features of hereditary cancer syndromes, a consideration of diagnoses, genetic testing if indicated and available, recommendations for the prevention and management of cancer, and information for at-risk relatives (Hampel et al., 2015). The American College of Surgeons (ACS) Commission on Cancer[3] has issued standards for

[3]For more information, see http://www.facs.org/cancer/coc/cocprogramstandards2012.pdf (accessed September 25, 2015).

the provision of cancer risk assessment, genetic counseling, and genetic testing services (ACS, 2012). Several other clinical societies and organizations have also developed guidelines and recommendations for when referrals should be made to cancer genetic consultation (see Table 3-3). With the exception of the U.S. Preventive Services Task Force (USPSTF), all of the organizations recommend that all women diagnosed with ovarian carcinoma receive referral for genetic counseling and testing regardless of their family history. Guidelines from the Society of Gynecologic Oncology (SGO), the National Society of Genetic Counselors (NSGC), the American College of Medical Genetics and Genomics (ACMG), and the NCCN all recommend referral to a cancer genetics professional for women without a personal history of cancer but with a family history strongly suggestive of hereditary breast and ovarian cancer (HBOC) (Lancaster et al., 2015; NCCN, 2015).

In spite of the benefits of germline genetic testing for women diagnosed with ovarian cancer, the rate of referral to genetic counseling and testing in accordance with existing guidelines still remains low (Febbraro et al., 2015; Powell et al., 2013a). For example, one study of women with ovarian cancer found that only 14.5 percent of women who should have been counseled according to NCCN guidelines actually were referred to genetic counseling (Febbraro et al., 2015). Further, only 59.5 percent of the women who were referred actually did follow up with the genetic counseling, although of those who did receive counseling, approximately 95 percent ultimately underwent genetic testing.

One objective of Healthy People 2020[4] is that a greater percentage of women with a significant family history of breast or ovarian cancer receive genetic counseling (HHS, 2013). From 2006 to 2010 the proportion of women receiving genetic counseling rose from 34.6 to 52.9 percent (HHS, 2013). While this was a large increase, still nearly half of all eligible women are not receiving the recommended counseling. There are various patient-, provider-, and system-level barriers that make cancer genetics referrals less likely, including patients being unaware of a family history of cancer, the limited time that providers have to collect family history, and referral criteria that are complex and that vary by group (Hampel et al., 2015).

Relying on a patient's family history alone to consider whether genetic testing should take place will inevitably overlook some women with inherited mutations that put them at risk for ovarian cancer. As mentioned previously, many women with inherited mutations do not have a significant family history for cancer. Furthermore, family history may not indicate a high risk for women with few close female relatives, women with female relatives who underwent risk-reducing surgery at early ages, women who may be adopted and thus do not know their biological family's cancer his-

[4]For more information, see http://www.healthypeople.gov (accessed September 18, 2015).

TABLE 3-3
Current Recommendations for Cancer Genetic Consultation and Germline Genetic Testing[a] for Individuals with Personal or Family History[b] of Ovarian Cancer, 2013–2015

	Criteria for Ovarian Cancer Patient				
Group	Diagnosis	Family History	Genes	Criteria for Relatives of the Ovarian Cancer Patient	References
NCCN	Invasive ovarian cancer (including fallopian tube and primary peritoneal cancer)	None required	Multiple genes	• Known deleterious *BRCA* mutation in family member • First- or second-degree relative with invasive ovarian cancer	NCCN, 2015
USPSTF	Criteria unclear	Criteria unclear	*BRCA1*, *BRCA2*	• Known deleterious *BRCA* mutation in family member • Utilize validated *BRCA* familial risk stratification models to determine if a referral is appropriate	CMS, 2015; Nelson et al., 2014
SGO	High-grade epithelial ovarian, tubal, or peritoneal cancer	None required	Multiple genes	• Known deleterious *BRCA* mutation in family member • First-degree relative with high-grade epithelial ovarian, tubal, or peritoneal cancer • Several close relatives with high-grade epithelial ovarian, tubal, or peritoneal cancer	Lancaster et al., 2015
ACMG and NSGC	Ovarian cancer (including fallopian tube and primary peritoneal cancer)	None required	Multiple genes	• Known mutation in cancer susceptibility gene • First-degree relative with ovarian, tubal, or peritoneal cancer	Hampel et al., 2015
ASCO	Epithelial ovarian, fallopian tube, or primary peritoneal cancer (most commonly HGSC)	None required	*BRCA1*, *BRCA2*	• No guidance provided related to relatives	Lu et al., 2014

[a] All of the above organizations and the ACS Commission on Cancer recommend that the process of germline genetic testing include pre- and post-test counseling with a physician, genetic counselor, or other health care provider with expertise in cancer genetics.

[b] Family history includes first- or second-degree relatives, and third-degree relatives in some recommendations.

NOTE: ACMG = American College of Medical Genetics and Genomics; ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; NSGC = National Society of Genetic Counselors; SGO = Society of Gynecologic Oncology; USPSTF = U.S. Preventive Services Task Force.

tory, or women who otherwise do not know the family health history of one or both parents (Lancaster et al., 2015).

Cascade Testing

Cascade testing is a sequential process of identifying and testing close blood relatives of individuals who are at increased risk for genetic conditions; the process minimizes the number of tests and costs (George et al., 2015). If an individual has a known deleterious mutation, further genetic testing of close blood relatives requires testing only for the specific mutation rather than testing for the entire gene or doing multigene testing. Only single-site testing is needed for family members unless they are in a population with common and known founder mutations, such as Ashkenazi Jews. For relatives who are negative for the specific mutation, it is likely that their risk of cancer and their offspring's risk of inheriting the mutation are no greater than the risk for the general population. For relatives who have the same mutation, the cascade testing continues with testing their close blood relatives, and so on. Asymptomatic women with a known mutation are often referred to as previvors (FORCE, 2008). Figure 3-1 illustrates how cascade genetic testing might be carried out for individuals at high risk for HBOC syndrome.

Several of the clinical societies and organizations in Table 3-3 recommend that biological relatives of an individual with a deleterious mutation for *BRCA1*, *BRCA2*, or the Lynch syndrome genes be referred for genetic consultation. The Centers for Disease Control and Prevention (CDC) also promotes cascade testing as an important public health intervention among family members at risk for HBOC syndrome and Lynch syndrome (Bowen et al., 2012).

Reproductive and Hormonal Risk Factors

A variety of reproductive and hormonal factors, including oral contraception, parity, infertility, endogenous hormones, and exogenous hormones, may increase or decrease a woman's risk of developing an ovarian cancer. For some of these factors, there is not yet a robust evidence base for their association with ovarian cancer risk, particularly by tumor subtype.

Oral Contraception and Parity

Among the most well-established risk factors for ovarian cancer are the use of oral contraceptives (OCs) and parity. One large study found a 20 percent decrease in the risk of ovarian cancer for every 5 years of OC use; the association was similar for serous, endometrioid, and clear cell types,

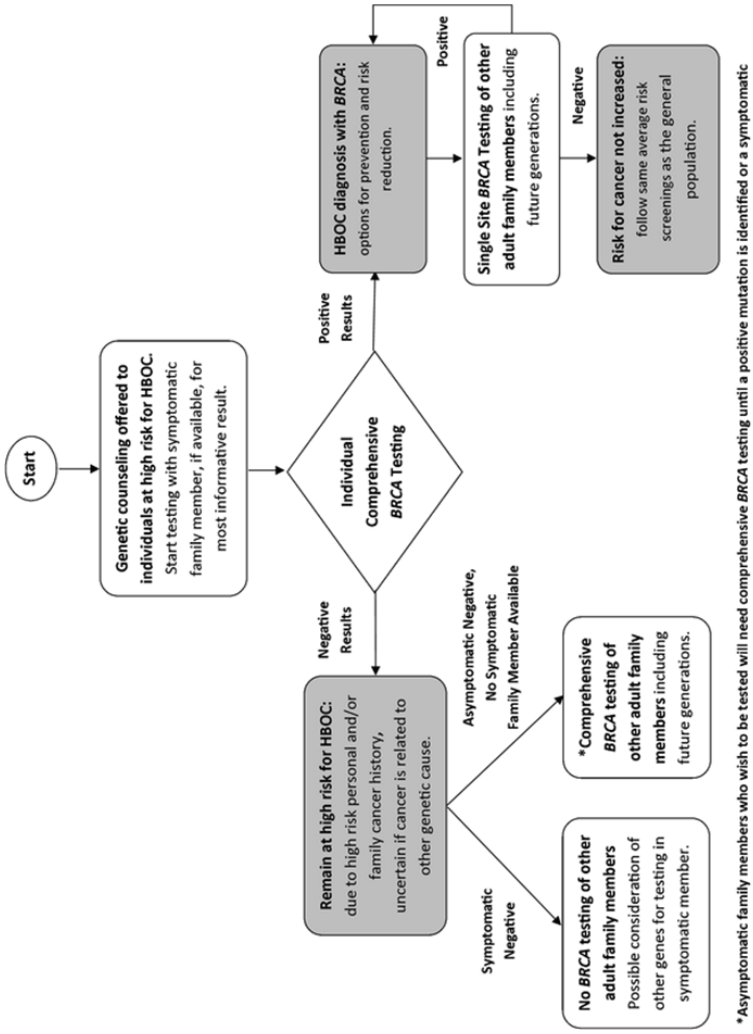

FIGURE 3-1 Cascade genetic screening of *BRCA* mutation for HBOC syndrome.
NOTE: HBOC = hereditary breast and ovarian cancer.
SOURCE: George et al., 2015.

although no association was observed for mucinous carcinomas (Beral et al., 2008). The protective effect of OCs waned with increasing time since last use and with later age at first use, suggesting that older women, who are at the highest risk, benefit less from prior OC use than younger women.

Parity is another clear protective factor for ovarian cancer. One analysis reported that the largest decrease in risk (approximately 30 to 40 percent) was associated with the first pregnancy, with about a 10 to 15 percent decrease in risk for each subsequent pregnancy (Whittemore et al., 1992). Age at first birth has not been consistently associated with risk, but later age at last birth may be weakly associated with decreased risk (Bevier et al., 2011). One meta-analysis suggests that breastfeeding among parous women reduces risk, with risk reduced by 8 percent for every 5 additional months of breastfeeding (Luan et al., 2013).

Most studies suggest that OCs and breastfeeding may reduce risk for all ovarian carcinoma types except mucinous carcinomas (Beral et al., 2008; Fortner et al., 2015; Gates et al., 2010; Merritt et al., 2013; Yang et al., 2012). Increasing parity only modestly reduces the risk for serous carcinomas or Type II tumors, but it significantly reduces the risk for endometrioid and clear cell carcinomas or Type I tumors (Setiawan et al., 2013).

Infertility

Most studies of infertility suggest that female-factor infertility is associated with a modestly increased risk for ovarian cancer (Tworoger et al., 2007). Many fertility drugs can increase the level of gonadotropins and ovulation, both of which are hypothesized to influence the risk for ovarian cancer. While the results have been somewhat inconsistent, several larger studies with long follow-up have found little or no association of clomiphene citrate (an ovulatory stimulant) or exogenous gonadotropins with ovarian cancer risk, although one study did find suggestive evidence of an increased risk for nulliparous women using clomiphene citrate (Jensen et al., 2009; Trabert et al., 2013).

Endometriosis, which is defined by the presence of endometrial tissue outside the uterine cavity, is a common cause of infertility and has been positively associated with ovarian cancer risk. One analysis of women with and without endometriosis found a two- to threefold increased risk for ovarian cancer, specifically for endometrioid and clear cell carcinomas, among women with endometriosis (Pearce et al., 2012). Other ovarian cancer subtypes, including HGSC and mucinous carcinoma, were not associated with endometriosis (though there was a suggestive association for low-grade serous carcinoma) (Guo, 2015; Pearce et al., 2012). These results support the hypothesis that endometriotic tissue may be a precursor lesion for certain ovarian cancer subtypes (see Chapter 2).

Polycystic ovarian syndrome (PCOS) has been hypothesized to be associated with ovarian cancer because of the increased levels of androgens that it produces and its association with infertility (Daniilidis and Dinas, 2009). However, several studies have found PCOS to have no associations with ovarian cancer risk, although there was a suggestive association among older women in one study (Barry et al., 2014; Gottschau et al., 2015; Shen et al., 2015).

Other Reproductive Factors

Other reproductive factors, such as age at menarche and age at menopause, have been weakly or inconsistently associated with ovarian cancer risk (Permuth-Wey and Sellers, 2009). However, the estimated number of ovulatory years (e.g., age at menopause minus age at menarche minus years of OC use and pregnancy) appears to be strongly positively associated with risk for all types of ovarian carcinoma (Fortner et al., 2015; Gates et al., 2010). Overall, these results suggest that ovulation and the associated hormonal and inflammatory process (e.g., ovarian surface epithelium repair after ovulation) are likely to be important in the etiology of ovarian carcinomas. The strong protective effect that pregnancy has for endometrioid and clear cell carcinomas suggests a potential role for progesterone exposure in these tumor types, although this has not been directly assessed.

Hormones

Steroid hormones are also thought to play a role in ovarian cancer risk (Lukanova and Kaaks, 2005). Androgens have been hypothesized to increase risk, for example, but most prospective studies of circulating androgens (e.g., testosterone, DHEA) have not observed an association, although one study did report an increased risk for Type I tumors—and a decreased risk for Type II tumors—with increasing androstenedione levels (Ose et al., 2015a; Risch, 1998; Tworoger et al., 2008b). One small study of endogenous hormones that included estrogen and progesterone found that neither of these hormones had a significant association with ovarian cancer risk, although a more recent study found that high estradiol levels during pregnancy were associated with an increased risk of endometrioid tumors (Helzlsouer et al., 1995; Schock et al., 2014b).

Experiments in cell and animal models indicate that the hormones insulin-like growth factor I (IGF-1) and placental growth hormone (GH) are expressed in the ovary and are involved in ovarian function or the progression of ovarian cancer (Beauchamp et al., 2010; Bruchim and Werner, 2013; Hull and Harvey, 2001). A study of IGF-1 and GH serum concentration from early pregnancy found that GH was not associated with risk for

ovarian carcinomas and that IGF-1 showed borderline significant associations, with a decreased risk for all ovarian carcinoma subtypes together as well as invasive and endometrioid tumors individually (with slightly stronger associations in women diagnosed under the age of 55) (Schock et al., 2015). Other hormones, such as prolactin and anti-Müllerian hormone, may be associated with ovarian cancer risk, but larger studies are needed (Clendenen et al., 2013; Schock et al., 2014a).

Further support for the role of hormones in ovarian cancer etiology includes the positive association observed between postmenopausal hormone replacements and increased ovarian cancer risk. In the largest prospective study to date, the use of any hormone therapy at any time was associated with a 20 percent increase in risk for ovarian cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015). The observed increase in risk was slightly stronger for the use of estrogen only (34 percent higher risk) than for the use of estrogen plus progestin (14 percent increased risk), and durations of hormone use of greater than 5 years were associated with the highest risk. Multiple studies have reported that hormone therapy is more strongly associated with risk for serous and endometrioid carcinomas than for other types, although one study found no difference in risk for Type I versus Type II cancers (Beral et al., 2015; Fortner et al., 2015; Gates et al., 2010; Yang et al., 2012).

Behavioral and Inflammatory Risk Factors

In general, lifestyle factors such as diet, physical activity, adiposity, and smoking have not been strongly associated with ovarian cancer risk. However, a number of recent smaller studies have found some evidence for the role of lifestyle factors in risk for ovarian cancer.

Diet

Studies of overall diet quality and dietary patterns have generally not shown an association with ovarian cancer risk; however, data from the low-fat dietary intervention in the Women's Health Initiative[5] indicated that there was a 40 percent lower risk for ovarian cancer in women who followed the low-fat dietary intervention for more than 4 years (Chandran et al., 2011; Chang et al., 2007; Edefonti et al., 2008, 2009; Kolahdooz et al., 2009; Prentice et al., 2007; Romaguera et al., 2012; Thomson et al., 2014; Xie et al., 2014). Several studies have reported that both total fat intake and polyunsaturated fat intake have modest positive associations with

[5] For more information on the Women's Health Initiative, see https://www.nhlbi.nih.gov/whi (accessed September 2, 2015).

ovarian cancer risk, although a pooled analysis of 12 prospective studies did not observe an association (Blank et al., 2012; Genkinger et al., 2006b; Merritt et al., 2014b). Studies on the risk associated with meat consumption have been inconsistent (Kolahdooz et al., 2010; Wallin et al., 2011).

Several studies have found no risk associated with overall lactose intake, but a single study did suggest that the intake of lactose and dairy foods is inversely associated with risk for endometrioid carcinomas (Cramer, 1989; Genkinger et al., 2006a; Liu et al., 2015; Merritt et al., 2014a). Increased consumption of tea and its components (e.g., flavonoids and caffeine) has been suggested to lower risk (Cassidy et al., 2014; Gates et al., 2009; Gosvig et al., 2015; Lueth et al., 2008; Rossi et al., 2008, 2010; Song et al., 2008; Tworoger et al., 2008a; Wang et al., 2009; Zhang et al., 2014). Studies of other dietary factors, including alcohol, fruits, vegetables, and vitamin intake, have not demonstrated any associations with ovarian cancer risk (Genkinger et al., 2006c; Koushik et al., 2005, 2006).

Adiposity and Body Size

Adiposity and body size are important lifestyle factors associated with a number of cancers (Renehan et al., 2015). While height is consistently associated with an increased risk of ovarian cancer, associations of ovarian cancer risk with various measures of adiposity have been inconsistent, possibly because of differences due to menopausal status (Aune et al., 2015). In one large study, only premenopausal ovarian cancer was positively associated with body mass index (BMI) (Schouten et al., 2008). One meta-analysis reported that higher adult BMIs were modestly associated with an increased ovarian cancer risk and that the risk was greater for higher BMIs in early adulthood (Aune et al., 2015). The risks associated with other measures of adiposity (e.g., waist and hip circumference) are not as well studied.

Physical Activity

Physical activity and sedentary behavior have been shown to be associated with risk of breast, colon, and other cancers (Phillips et al., 2015). However, physical activity has not been clearly or consistently associated with ovarian cancer risk; it is possible that the association is different for premenopausal versus postmenopausal activity (Huang et al., 2015a; Zhong et al., 2014). Several studies have reported conflicting results as to whether measures of a sedentary lifestyle (e.g., total sitting or the amount of time spent watching television) are associated with an increased risk of ovarian cancer (Hildebrand et al., 2015; Patel et al., 2006; Xiao et al., 2013; Zhang et al., 2004).

Smoking

The association of smoking with risk for ovarian cancer varies by subtype. A recent meta-analysis found a 7 percent increased risk of ovarian cancer for current smokers versus women who had never smoked, but the association varied significantly by histologic subtype (Beral et al., 2012). Smoking was associated with an approximately 20 percent lower risk for endometrioid and clear cell carcinomas and an approximately 80 percent increased risk for mucinous carcinomas among current smokers versus never-smokers; serous carcinomas were not associated with smoking.

Inflammation

Studies of the inflammatory marker C-reactive protein suggest a possible association between inflammation and an increased risk of ovarian cancer (Ose et al., 2015b; Poole et al., 2013). Other specific inflammatory factors have also been associated with ovarian cancer. A meta-analysis reported that exposure to asbestos was associated with a 77 percent increased risk of ovarian cancer mortality (Camargo et al., 2011), and the International Agency for Research on Cancer determined that there was sufficient evidence to support a causal relationship between asbestos exposure and ovarian cancer (Straif et al., 2009). This has led to studies of talc use, which is chemically similar to asbestos and can cause an inflammatory response. The use of perineal talcum powder has been associated with a 20 to 30 percent increased risk of ovarian cancer, although it also has been show to vary by histologic subtype (Cramer et al., 2015; Terry et al., 2013). One analysis reported a 9 percent lower ovarian cancer risk with regular aspirin use, with stronger results among daily users (Trabert et al., 2014). However, most cohort studies have not observed a similar reduction in risk (Brasky et al., 2014; Lacey et al., 2004; Murphy et al., 2012; Ni et al., 2013; Pinheiro et al., 2009; Prizment et al., 2010; Setiawan et al., 2012).

As mentioned previously, endometriosis is associated with an increased risk of ovarian cancer, and tubal ligation and hysterectomy (which may limit the ability of endometrial tissues to access the fallopian tubes, ovaries, and pelvic region by retrograde menstruation) act to decrease this risk. Hysterectomy is associated with an approximately 30 percent decreased risk of ovarian cancer, and tubal ligation has been associated with a 26 percent decreased risk of ovarian cancer overall and a 55 percent lower risk of endometrioid cancer, the ovarian cancer type most strongly associated with endometriosis (Rice et al., 2012). The exact causes for the increased risk of ovarian cancer from endometriosis are unknown. However, endometriosis is associated with an inflammatory environment characterized by elevated levels of cytokines and growth factors (Arici, 2002; Malutan

et al., 2015a,b). This pro-inflammatory environment may produce an environment favorable for tumor development and growth (Hanahan and Weinberg, 2011). As previously discussed, endometriosis is associated with infertility and nulliparity, which may further increase the risk of ovarian cancer.

Other conditions that increase local peritoneal inflammation may also be associated with ovarian cancer risk. Studies of the association of chronic pelvic inflammatory disease (PID), which develops from sexually transmitted infections, and ovarian cancer risk have had mixed results (Lin et al., 2011; Ness et al., 2000; Parazzini et al., 1996; Rasmussen et al., 2013; Risch and Howe, 1995; Rowlands et al., 2011; Shu et al., 1989). However, PID was not uniformly defined in these studies, which may have led to misclassifications. In some studies, serologic evidence of chlamydia infection, a common cause of PID, has been associated with an increased ovarian cancer risk, particularly for cancer arising in the fallopian tube (Idahl et al., 2011; Ness et al., 2003, 2008).

Psychological, Social, and Environmental Risk Factors

Experimental evidence suggests that psychosocial stress can influence processes that may be relevant to ovarian cancer development, such as inflammation and wound healing (Kiecolt-Glaser et al., 2010; Powell et al., 2013b; Walburn et al., 2009) For example, in a study of mice with a Trp53 gene mutation, chronic stress led to increased tumor incidence and decreased latency (i.e., time from exposure to tumor growth) (Feng et al., 2012). Although ovarian tumors were not studied explicitly, there is a clear link between *TP53* alterations and ovarian cancer (see Chapter 2). Furthermore, mice subjected to physical restraint or social isolation and injected with ovarian cancer cells were shown to have more than twice the tumor weight and nodule count than found in controls that had been injected with cancer cells but not stressed; half of all the stressed mice had metastases versus none in the controls (Thaker et al., 2006). Specifically, norepinephrine, a stress hormone, has been shown to alter cell adhesion, migration, invasion, and angiogenesis in stressed mice (Armaiz-Pena et al., 2013; Thaker et al., 2006). Norepinephrine also increases the invasive potential of the cells and the expression of vascular endothelial growth factor (Nilsson et al., 2007; Sood et al., 2006).

The role that chronic stress and its biologic response play in ovarian carcinogenesis is understudied in human populations. One meta-analysis found that reports of psychosocial stress were modestly, but significantly, associated with a 6 to 20 percent increase in overall cancer risk; the associations were stronger in studies with large sample sizes and long follow-up (Chida et al., 2008). A recent prospective study found that women with

depressive symptoms had a significant 30 percent higher risk of ovarian cancer (Huang et al., 2015b). Very little research has been conducted on the association between socioeconomic status and ovarian cancer risk. One study in Denmark suggested a positive association between disposable income and ovarian cancer risk, but no other socioeconomic indicators were associated with risk (Jensen et al., 2008).

RISK FACTORS AND TUMOR SUBTYPES

While some factors affect risk for all ovarian cancer subtypes, many factors appear to affect risk for different ovarian cancer subtypes in different ways, including increasing risk for one or more subtypes and decreasing risk for others (Yang et al., 2012). Generally, studies have used histology with or without tumor grade as a surrogate for tumor type. The inability to demonstrate clear associations for certain risk factors may be due in part to the limited power of individual studies to assess associations by tumor type.

The complex associations that these factors have with ovarian cancer risk are driven in part by the differing etiologies for the diverse ovarian cancer subtypes. Many of the studies described earlier in this chapter used the Type I and Type II classification dichotomy. This schema has greater power to detect associations (by increasing the number of cases in each category), but it ignores the unique biology of each subtype and thereby likely masks particular associations.

RISK PREDICTION MODELS

Risk prediction models for women at average genetic risk are important tools for informing women of their 5- and 10-year risk for ovarian cancer, for improving clinical decision making, and for identifying women for enrollment in prevention studies (Freedman et al., 2005). Table 3-4 outlines four studies that have developed risk prediction models for ovarian cancer among women at average genetic risk. Overall, these studies do not demonstrate a strong predictive ability that would be meaningful in clinical decision making, most likely because of the relative rarity of ovarian cancer and the somewhat modest effect sizes of the known risk factors. Improving the discriminatory ability of these models will likely require the consideration of differential associations by tumor subtype and the identification of new risk factors.

PREVENTION STRATEGIES

Most medical strategies designed to prevent the occurrence of ovarian cancer are structured around modulating female hormone cycles and the

TABLE 3-4
Risk Prediction Models for Ovarian Cancer in Average Risk Populations

References	Study Used to Develop Model	Validation of Model	Risk Factors Included in Risk Prediction Model	AUC[a]
Hartge et al., 1994	Seven case-control studies	No	Parity, OC use, family history of breast or ovarian cancer	None provided
Rosner et al., 2005	Nurses' Health Study I and II	Yes	Estimated ovulatory years (incorporates parity and OC), duration of menopause, tubal ligation	0.60
Pfeiffer et al., 2013	PLCO screening trial, NIH-AARP Diet and Health Study	Yes	Parity, OC use, family history of breast or ovarian cancer, menopausal hormone use	0.59
Li et al., 2015	European Prospective Investigation into Cancer and Nutrition	Yes	Parity, OC use, menopausal status, age at menopause, menopausal hormone use, unilateral oophorectomy, BMI	0.64

NOTE: AUC = area under the curve; BMI = body mass index; NIH = National Institutes of Health; OC = oral contraceptive; PLCO = prostate, lung, colorectal, and ovarian.

[a]An AUC of 0.5 predicts outcomes no better than chance (generally an AUC greater than 0.7 may be considered for clinical use).

surgical removal or modification of gynecological tract components, including the fallopian tubes (salpingectomy), ovaries (oophorectomy), and uterus (hysterectomy).

Bilateral Salpingo-Oophorectomy (BSO)

BSO, also known as risk-reducing salpingo-oophorectomy (RRSO), is the surgical removal of the fallopian tubes and ovaries, which dramatically reduces the risk of ovarian cancer in women at average risk and high risk due to inherited genetic susceptibility (see Table 3-5). The USPSTF and SGO advocate RRSO for women at high genetic risk, but it may also be effective for women at average or unknown genetic risk (Evans et al., 2009; Nelson et al., 2014; Walker et al., 2015). The GOG-0199 study, also known as the National Ovarian Cancer Prevention and Early Detection Study, a number of factors linked to a higher risk of ovarian cancer were found during RRSO, including being postmenopausal or having mutated *BRCA1* or *BRCA2* genes, abnormal CA-125 test results, and abnormal transvaginal ultrasound (TVU) results (Sherman et al., 2014). However, the

TABLE 3-5
Risk Reduction After Bilateral Salpingo-Oophorectomy

Genetic Risk	Study	Number of Subjects	Relative Risk of Ovarian Cancer With vs. Without RRSO (95% confidence interval)	Risk Reduction (%)
High (*BRCA1* or *2* positive)	Rutter et al., 2003	249	0.29 (0.12–0.73)	71
	Finch et al., 2006	1,828	0.20 (0.07–0.58)	80
	Finkelman et al., 2012	3,787	0.08 (0.04–0.16)	92
Average or low	Rutter et al., 2003	598	0.05 (0.01–0.22)	95
	Parker et al., 2009[a]	29,390	0.04 (0.01–0.09)	96
	Jacoby et al., 2011[a]	25,448	0.07 (0.02–0.22)	93
Unknown	Evans et al., 2009	803	0.08 (0.01–0.57)	92

[a]Only among women with a hysterectomy.

risk reduction achieved with RRSO is not 100 percent, and the procedure is not without inherent risks and side effects, including early menopause, osteoporosis, cardiovascular disease, and increased overall mortality (Finch et al., 2014). As such, no formal body has recommended RRSO for the primary prevention of ovarian cancer for the general population.

Bilateral Salpingectomy with Ovarian Retention (BSOR)

To avoid the long-term complications associated with removing the ovaries, BSOR, a surgical procedure that removes the fallopian tubes but leaves the ovaries intact, may prove to be a valuable option for women at risk for developing ovarian cancer (Daly et al., 2015). There is a growing evidence base suggesting that the various ovarian carcinoma subtypes have different sites of origins (see Chapter 2). However, the proportion of ovarian cancers that originate from sites outside the ovaries is unknown, and therefore the effectiveness of BSOR in preventing ovarian cancer is uncertain and may differ by subtype. For example, BSOR may be most effective in preventing the ovarian carcinoma subtypes postulated to arise in the fallopian tubes. Furthermore, BSOR can prevent retrograde menstrua-

tion of endometrial tissue, which is thought to be the origin and cause of endometriosis and possibly to be associated with endometrioid and clear cell carcinomas, as discussed in Chapter 2 (Leblanc et al., 2011; Salamanca and Beltran, 1995; Sampson, 1927; Sanfilippo et al., 1986).

BSOR might allow high-risk women to delay removal of ovaries until the procedure is desired or warranted. For average-risk women, BSOR at the time of a planned hysterectomy may be a prevention opportunity. Until recently, salpingectomy was typically not performed as part of a standard hysterectomy unless the ovaries were also being removed. Data suggest that a salpingectomy at the time of hysterectomy is feasible, safe, and does not affect short-term ovarian function (McAlpine et al., 2014). However, establishing the safety and efficacy of this procedure will require additional data from more women with a longer follow-up.

Recent population-based studies suggest that salpingectomy may reduce the incidence of ovarian cancer in the general population (Falconer et al., 2015; Guldberg et al., 2013). In a study from Sweden, salpingectomy (indicated for medical reasons) was associated with a 35 percent reduction in ovarian cancer risk (Falconer et al., 2015). A second study reported no significant reduction in risk for unilateral salpingectomy, but a 42 percent reduction in risk for BSOR (Madsen et al., 2015). However, these results were based on a small number of cases, and neither study had sufficient cases to assess the association by histologic subtype. In light of the evidence of the distal fallopian tube epithelium as the site of origin of at least some HGSCs, the SGO and American Congress of Obstetricians and Gynecologists have issued statements recommending consideration of opportunistic BSOR to reduce ovarian cancer mortality in the general population (ACOG Committee on Gynecologic Practice, 2015; SGO, 2013).

Tubal Ligation

Tubal ligation, a surgical procedure in which the fallopian tubes are tied or blocked in such a way that eggs released from the ovary cannot reach the uterus, reduces the risk for ovarian cancer in both high-genetic-risk and average-genetic-risk populations (Rice et al., 2012). One meta-analysis found that the risk for ovarian cancer for women who underwent tubal ligation dropped by 33 percent compared with women who did not undergo surgery (Cibula et al., 2011). The reduction in risk is associated primarily with the endometrioid and clear cell histologic subtypes and appears to last for up to 14 years post-surgery (Madsen et al., 2015; Rice et al., 2013; Sieh et al., 2013). Similar reductions in risk have been reported among *BRCA1* mutation carriers in whom HGSCs are the most common subtype of ovarian cancer (Antoniou et al., 2009; Narod et al., 2001).

Hysterectomy

Women who have undergone a hysterectomy, the surgical removal of the uterus, have a lower risk of ovarian cancer (Rice et al., 2012; Vitonis et al., 2011). As noted earlier, endometriosis is associated with increased peritoneal inflammation and is commonly associated with endometrioid carcinoma and clear cell carcinoma (Arici, 2002; Leblanc et al., 2011; Malutan et al., 2015a,b). A hysterectomy may prevent ovarian cancer by limiting the ability of endometriotic tissue to access the fallopian tubes and the ovaries through retrograde menstruation, thereby stopping the associated inflammation and protumorigenic environment. Thus, a hysterectomy may prevent the development of certain types of ovarian cancer, but no formal body has recommended hysterectomy as a prevention strategy.

Prescription Medications

One of the primary alternatives to surgical intervention for the prevention of ovarian cancer is use of hormone-modulating prescription drugs such as OCs. The amount or type of hormones (i.e., estrogen and progestin) in OCs can affect ovarian cancer risk. However, research has produced conflicting results on the effects of the various types of hormones present in OCs (Greer et al., 2005; Hankinson et al., 1992; Schildkraut et al., 2002). As was noted earlier in this chapter, OCs have consistently been associated with a lower risk of ovarian cancer, including a reduction in the risk for nearly all histologic subtypes. One analysis estimated that two ovarian cancer cases and one ovarian cancer–related death are prevented for every 500 woman-years of OC use (Beral et al., 2008). The analysis further estimated that in developed countries, where ovarian cancer incidence is high and OC use is very common, approximately 13 percent of the ovarian cancer that would have occurred in women younger than age 75 is prevented by OC use. But there are also some risks associated with OC use, including a slightly increased breast cancer risk and a two- to threefold higher risk of venous thromboembolism and ischemic stroke (Bassuk and Manson, 2015; Havrilesky et al., 2013). These associations, however, are primarily related to the current use of OCs, and the diseases whose risks are increased by OC use are relatively rare in young women (Bassuk and Manson, 2015).

The SGO has stated that OCs "reduce the risk of ovarian cancer for average-risk women and *BRCA1* and *BRCA2* mutation carriers. Appropriate counseling about side effects and contraindications will allow each patient to weigh the risks and the benefits" (Walker et al., 2015, p. 2116). However, the CDC has concluded that insufficient evidence is available to address the use of OCs in ovarian cancer prevention (Havrilesky et al., 2013).

EARLY DETECTION

As discussed in Chapter 1, one of the chief causes of the significant morbidity and mortality from ovarian cancer is the late stage at which most women are diagnosed (see Figure 1-5), which is partly due to the lack of clear and unique ovarian cancer–specific symptoms. Because of this absence of specific symptoms, researchers have investigated other strategies for early ovarian cancer detection, such as assaying for one or more biomarkers, often in combination with imaging technologies. While the use of these strategies in large screening trials has resulted in more women being diagnosed with ovarian cancer at earlier stages, to date these strategies have not reduced overall mortality. Furthermore, because some ovarian carcinoma subtypes originate away from the ovaries, it is difficult to know where to look to detect the earliest lesions associated with ovarian cancer. Because this is an issue specific to ovarian cancer, it is difficult to draw on early detection methods from other heterogeneous cancers. Thus developing effective and reliable early detection strategies for ovarian cancer will require ongoing research aimed at better understanding the early molecular and genetic events associated with the carcinogenesis of each subtype of ovarian cancer, along with better assessment of disease-specific symptoms.

Biomarkers

A biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition" (NCI, 2015). Although the most commonly used biomarkers in clinical care are proteins, the definition includes a broad spectrum of biochemical substances, including nucleic acids (e.g., DNA and various types of RNA), lipids, small metabolites, and even whole cells (IOM, 2007). Biomarkers are used throughout the cancer care continuum. Predictive biomarkers are used in risk assessment and to measure the biological response to an intervention, and prognostic biomarkers are used to describe outcomes such as progression-free or overall survival (Huang et al., 2010; IOM, 2007). In research on ovarian cancer, the most extensively studied and frequently used biomarkers are two proteins, cancer antigen 125 (CA-125) and human epididymis protein 4 (HE-4). The following sections discuss how these and other biomarkers have affected our understanding of ovarian cancer risk and describe these biomarkers' utility in screening and early detection.

CA-125

CA-125 gained prominence following a study that identified an antibody against CA-125 that reacted predominantly with malignant ovarian tissue (Bast et al., 1981). Nearly 80 percent of women with an advanced (Stage III or IV) ovarian carcinoma have elevated CA-125 serum levels at diagnosis (Niloff et al., 1984). Research that followed up on the original study found that serum levels of CA-125 correlate both with disease stage and with the response to chemotherapy, suggesting that CA-125 could be useful as a marker of disease progression as well as a prognostic biomarker (Bast et al., 1983; Hawkins et al., 1989; Hising et al., 1991; Kobayashi et al., 2012). CA-125's potential use as a tool in early detection was extrapolated from these studies and also case reports noting its rise in asymptomatic women in advance of being diagnosed with ovarian cancer (Bast et al., 1985).

The biology behind CA-125's apparent association with ovarian cancer risk and prognosis is currently unclear. Laboratory research suggests that CA-125 may play roles in metastasis to the peritoneal cavity and in promoting chemoresistance to several drugs that are used in standard ovarian cancer chemotherapy protocols, but these findings have not been replicated clinically (Boivin et al., 2009; Felder et al., 2014; Gubbels et al., 2006).

For early detection, CA-125 is a predictive tool that becomes increasingly powerful with proximity to diagnosis and may signal the presence of precursor lesions (Jacobs et al., 1999). Using trends in CA-125 levels to select women for imaging may improve its screening performance (Karlan et al., 2014). This strategy is currently being tested in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Several algorithms developed over the past decade can help predict the presence of ovarian cancer in women with a pelvic mass so that they may be triaged to appropriate specialists (i.e., gynecologic oncologists). The majority of these algorithms have incorporated CA-125 along with other biomarkers or diagnostic indicators (e.g., OVA-1, the Risk of Ovarian Malignancy Algorithm [ROMA], and the Risk of Malignancy Index) (Bast et al., 2012; Cohen et al., 2014; Jacobs et al., 1990; Moore et al., 2009; Skates et al., 1995).

Challenges with the use of CA-125 for early detection of or screening for ovarian cancer include its lack of specificity and sensitivity. For example, CA-125 may be markedly elevated in patients who have a variety of benign or nonovarian malignant conditions, and in approximately 20 percent of women with ovarian cancer it is expressed not at all or only in trace amounts (Cohen et al., 2014; Miralles et al., 2003; Moore et al., 2008). Finally, serum levels of CA-125 are significantly elevated above baseline in only half of women diagnosed with early stage (Stage I or II) ovarian cancer (Woolas et al., 1993).

HE-4

A 1999 study looking for genes that are significantly overexpressed in ovarian tumors when compared with normal ovarian tissue singled out WFDC2, which encodes the HE-4 protein, as a potential diagnostic marker for ovarian cancer (Schummer et al., 1999). Subsequent research confirmed this expression pattern in ovarian carcinomas, and additional work in cell and animal models suggested a role for HE-4 in mediating resistance to chemotherapy and promoting tumor growth (Moore et al., 2014; Welsh et al., 2001). Compared with CA-125, HE-4 has a similar sensitivity for detecting late-stage ovarian cancer but a greater specificity in differentiating between malignant and benign tumors (Bast et al., 2005). In 2011, the U.S. Food and Drug Administration (FDA) approved the use of ROMA, which combines measurements of HE-4 and CA-125 with menopausal status to determine whether a woman presenting with a pelvic mass is at a high or low risk of malignancy (Moore et al., 2009, 2011). However, as is the case with CA-125, elevated serum levels of HE-4 are not unique to women with ovarian tumors and are found in individuals with tumors of gynecologic and pulmonary origin (Drapkin et al., 2005; Karlsen et al., 2014). Nonetheless, the dramatic increases in HE-4 serum concentration seen in women with ovarian carcinomas (and in the serous and endometrioid subtypes in particular) support its usefulness as a biomarker with high specificity for the early detection of ovarian cancer (Escudero et al., 2011; Hertlein et al., 2012; Karlsen et al., 2014).

Other Ovarian Cancer Biomarkers

As described in Chapter 2, microRNAs (miR) appear to play a role in several biological processes related to ovarian cancer. A number of microRNAs are expressed at either a higher or lower level in ovarian cancer tissue than in normal ovarian surface epithelium, and they also differ in their levels of expression among the various ovarian cancer subtypes (Lee et al., 2009; Zhang et al., 2015). The altered levels of several of these microRNAs can be detected in a woman's peripheral blood and may serve as early detection biomarkers alone or in tandem with other commonly used biomarkers (Taylor and Gercel-Taylor, 2008; Zhang et al., 2015).

Advances in protein and nucleic acid analysis technologies such as microfluidic chips, nuclear magnetic resonance, and other high-throughput platforms make possible the analysis of small amounts of patient-derived samples for numerous potential biomarkers. The ovarian cancer sample sources that are currently investigated include tumor cells in ascites (i.e., fluid that accumulates in the peritoneal cavity after metastasis), circulating tumor cells in the blood, and exosomes (i.e., small membrane-bound vesicles secreted by cancer cells into bodily fluids) (Castro et al., 2015).

Biomarker Tests

FDA-approved protein tumor markers include ROMA (HE-4 and CA-125), OVA-1 (measures levels of apolipoprotein A1, beta 2 microglobulin, CA-125, prealbumin, and transferrin), HE-4, and CA-125 (Fung, 2010; Moore et al., 2010; Moss et al., 2005; Muller, 2010; Wu et al., 2012). Although a great deal of research is being carried out on identifying and developing new biomarkers for ovarian cancer, scientists often find it difficult to navigate the analytical, diagnostic, and regulatory requirements for a clinical assay (Fuzery et al., 2013). Currently, none of the FDA-approved protein tumor markers are approved as screening tests for ovarian cancer.

Imaging Technologies for Early Detection

Imaging technologies help measure the size of tumors and the extent to which they have spread after the masses have been detected during a clinical examination, and these same technologies may have a role to play in earlier detection of ovarian cancer. Most of these technologies are noninvasive or minimally invasive and may be performed in the outpatient setting using no anesthesia or only local anesthesia. The most common imaging technologies used for ovarian cancer are ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Modifications to these technologies that incorporate radiologic markers or sound waves have improved image quality and resolution, and some newer techniques may enable up-close visualization of tumor growth in the fallopian tubes and on the ovary surfaces.

Transvaginal Ultrasound

TVU (also known as transvaginal sonography) is the most widely used imaging technique for the examination of pelvic organs (Manegold-Brauer et al., 2014). TVU is used primarily to evaluate gynecologic symptoms and pathologies, including pain or pressure in the pelvic region, irregular bleeding, fibroids, and adnexal masses (e.g., ovarian cysts, ectopic pregnancies, and tumors near the uterus). While TVU can identify most adnexal masses, the majority of these masses are benign, and TVU is limited in its ability to differentiate between malignant tumors and benign tumors. Overall, TVU has not yet shown value as a primary screening tool for ovarian cancer, but it may be useful with specific populations (e.g., women at high risk) or in conjunction with biomarkers for ovarian cancer screening (van Nagell et al., 2007).

Doppler and contrast-enhanced ultrasound techniques have been added to routine TVU to provide information on tissue vascularity and

angiogenesis in an effort to improve the ability to differentiate between benign and malignant masses. However, studies using Doppler imaging with TVU for ovarian cancer screening have revealed a wide range of specificities and a lower sensitivity than TVU alone (Kinkel et al., 2000). The use of non-targeted and targeted microbubbles to distinguish benign from malignant ovarian lesions is still in the investigational stage (Lutz et al., 2011).

Magnetic Resonance Imaging

MRI is commonly used for a number of diseases and disorders, and it may be useful for the diagnosis and staging of adnexal masses (Manegold-Brauer et al., 2014). One meta-analysis found a 91.9 percent sensitivity and 88.4 percent specificity for classifying adnexal masses as malignant (Dodge et al., 2012). These values are similar to the sensitivity (96.0 percent) and specificity (90.0 percent) of TVU for classifying adnexal masses as malignant (Timmerman et al., 1999). As a result, TVU is often the first choice to identify masses, although MRI is useful to determine malignant potential of these masses when TVU may be unreliable (Dodge et al., 2012).

Computed Tomography

While CT scanning is commonly used in the management of ovarian cancer, it is primarily used as a staging tool. However, the early stages of ovarian cancer development may be readily missed by CT alone as its ability to distinguish benign from malignant masses is lower that that of MRI or TVU (Alt et al., 2011; Bharwani et al., 2011).

^{18}F-fluoro-deoxyglucose Positron Emission Tomography (^{18}F-FDG-PET)

An improved understanding of the role of glucose metabolism in tumor development has led to the use of glucose-based positron emission tomography (^{18}F-FDG-PET) for tumor imaging. While basic functional imaging techniques such as PET can detect actively growing masses, distinguishing between benign and malignant lesions is better done with ^{18}F-FDG-PET combined with CT scanning (^{18}F-FDG-PET/CT) (Manegold-Brauer et al., 2014; Yamamoto et al., 2008). Only a few studies have examined the usefulness of this technique for ovarian cancer screening, and early results indicate there is a high likelihood of missing borderline and low-grade tumors when using ^{18}F-FDG-PET/CT (Castellucci et al., 2007; Risum et al., 2007; Yamamoto et al., 2008).

CHALLENGES TO EARLY DETECTION OF OVARIAN CANCER

Because of the marked heterogeneity of ovarian carcinomas, it is likely that no single tumor biomarker will be sufficient to aid in the early detection of all the histologic subtypes. Research shows, for instance, that the distinct carcinoma subtypes express different sets of post-translationally modified proteins and microRNAs (Hua et al., 2013; Lee et al., 2009). There are also questions concerning the timing and type of patient samples that will need to be collected in clinical studies, although one screening trial suggests that serial biomarker measurements have better predictive power than single-time-point sampling (see detailed discussion in next section) (Cohen et al., 2014; Menon et al., 2015). It is becoming clearer that a more individualized approach to measuring CA-125 may be needed rather than having a single threshold for all women (Skates et al., 2011). This individualized approach could include longitudinal biomarker, genetics, and epidemiologic results in order to more accurately assess the risk for ovarian cancer. Another outstanding challenge is determining which marker or combination of markers meets the sensitivity and specificity requirements for early detection of a rare and heterogeneous disease. The difficulties of performing such validation studies are exacerbated by the low incidence of ovarian cancer, especially when separating out the different subtypes. However, recent screening trials (e.g., GOG-0199) actively collected DNA, serum, plasma, and tissue samples from high-risk women, which resulted in a valuable repository of samples for future studies (Greene et al., 2008).

Several challenges stand in the way of developing reliable and accurate early detection technologies for ovarian carcinomas. Imaging technologies have improved markedly over the years—including becoming less invasive and providing finer resolution of images—but a major challenge remains in the incomplete understanding of early carcinogenesis. While other types of cancer also have multiple subtypes, ovarian cancer is distinct in that the different subtypes likely develop from different tissues of origin. Once researchers have a better understanding of the cell of origin for each of the ovarian carcinoma subtypes, they may then have more success with the use of imaging technologies to find these ovarian carcinomas at earlier stages.

SCREENING FOR OVARIAN CANCER

Screening—checking for disease when there are no symptoms (NCI, 2015)—is a key tool in the early detection of disease. In general, the effectiveness of a screening test is evaluated in terms of the ability of the test to identify those individuals who truly have the disease in question and to rule out those individuals who do not have the disease. Furthermore, a standard goal is that no more than 10 exploratory diagnostic operations are

performed for every 1 actual case of ovarian cancer (Bast, 2003). Establishing these minimum targets is important primarily to avoid an unacceptable level of unnecessary and potentially harmful surgical or chemotherapeutic interventions (Etzioni et al., 2013; Jacobs and Menon, 2004).

No reliable screening method exists to detect ovarian cancer at earlier stages, and, as a result, no professional organization recommends screening in the general population. Current methods for detecting ovarian cancer include physical examination, assessment of symptoms, imaging methods (e.g., TVU), and the use of serum levels of CA-125 (as described previously) (Bast et al., 1998; Fishman et al., 2005; Higgins et al., 1990; Kinkel et al., 2000).

Ovarian Cancer Screening Trials

Early detection screening trials evaluate the effectiveness of screening strategies in reducing the morbidity and mortality from a disease. General screening strategies have proved to be effective in detecting early-stage disease for several forms of cancer (e.g., breast and colon cancer) in both general and high-risk populations (Nelson et al., 2009; Schoen et al., 2012). However, there is limited evidence to suggest that these strategies significantly decrease the short- or long-term mortality from these cancers (Harding et al., 2015). Several large trials have been conducted to determine whether screening for ovarian cancer within either the high-risk or the general population helps reduce mortality from the disease (see Table 3-6).

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which used CA-125 screening and TVU, showed no reduction in disease-specific mortality in women at average risk for ovarian cancer (Buys et al., 2011). However, an increase in invasive medical procedures and associated harms was observed. One limitation of this study was its use of a single fixed cutoff for CA-125 serum levels. Follow-up modeling studies of the PLCO study's results suggest that nearly 20 percent of ovarian cancer could have been detected at an earlier point if a CA-125 level trajectory had been taken into account that used the risk ROCA employed in later trials, although using the trajectory would have not affected mortality (Buys et al., 2011; Drescher et al., 2013; Pinsky et al., 2013). ROCA is based on annual measurements of CA-125 evaluated in a serial fashion so that each woman serves as her own baseline (Menon et al., 2005).

To study the predictive value of biomarkers beyond CA-125, the PLCO trial distributed sets of Phase III patient serum samples that were collected prior to the clinical diagnosis of ovarian cancer (Cramer et al., 2011). Al-

TABLE 3-6
Ovarian Cancer Prospective Screening Trials Results Summary

Study	Study Design	Screening Cohort Size	Screening Strategy	Interpretation of CA-125	Sensitivity (%)	Mortality/ Surrogate Results	References
PLCO	RCT, general population	30,630	CA-125 and TVU	Fixed cutoff, 35 U/mL	OC/FT: 69.5 IOC/FT: 68.2	No mortality benefit	Buys et al., 2011
UKCTOCS	RCT, general population, two arms	101,247	1. CA-125 followed by MMS 2. TVU only	ROCA (longitudinal sampling)	OC/FT: MMS (89.4)/ TVU (84.9) IOC/FT: MMS (84.9)/ TVU (75.0) IOC/FT: MMS (88.6)/ TVU (65.8)	Relative mortality reduction in MMS (14%) and USS (11%) groups over no screening, but reductions were not significant in the primary analysis	Jacobs et al., 2015; Menon et al., 2015
Japanese Shizuoka Cohort	RCT, low-risk postmenopausal	41,688	Physical exam, CA-125, and TVU	Fixed cutoff, 35 U/mL	OC/FT: 77.1	Stage shift; Stage I OC in screened (63%) versus control (38%)	Kobayashi et al., 2008
Kentucky Screening Study	Single-arm prospective, general population	25,327	TVU	None	OC/FT: 81 IOC/FT: 76.3	5-year survival in screened (74.8%) versus unscreened (53.7%)	van Nagell et al., 2007

NOTE: CA-125 = cancer antigen 125; IOC/FT = invasive cancer or fallopian tube; MMS = multimodal screening; OC/FT = ovarian cancer or fallopian tube cancer; PLCO = prostate, lung, colorectal, and ovarian cancer screening; RCT = randomized controlled trial; ROCA = risk of ovarian cancer algorithm; TVU = transvaginal ultrasound; UKCTOCS = United Kingdom Collaborative Trial of Ovarian Cancer Screening; USS = ultrasound scanning.

SOURCE: Adapted from Menon et al., 2014.

though researchers analyzed 35 different biomarkers that had been identified in PLCO trial specimens for use in ovarian cancer screening, CA-125 remained the single best biomarker among the samples tested (Cramer et al., 2011).

United Kingdom Collaborative Trial of Ovarian Cancer Screening

The UKCTOCS is the largest randomized controlled ovarian cancer screening trial to date, with 200,000 women enrolled and each assigned to one of three arms in order to compare two screening strategies (Sharma et al., 2012). The first strategy used ROCA to evaluate the trajectory of CA-125 serum concentration over time, starting from a baseline concentration (measured prior to diagnosis) and using concentrations measured annually throughout the 10-year screening period (Skates et al., 1995, 2001). This longitudinal sampling contrasts with the single fixed cutoff used in previous screening trials. In the first screening arm, the CA-125 trajectory was evaluated, and TVU was used as a second line test for women who had significantly elevated CA-125 levels. The second screening arm used only an annual TVU imaging, while the third, control arm used no intervention at all. In addition to evaluating patient survival, the UKCTOCS collected data on the cost of screening, acceptance of screening modalities by patients, and a variety of physiological and psychosocial comorbidities linked to screening with TVU and measuring CA-125 levels.

The UKCTOCS found that using ROCA and TVU resulted in a notable improvement in the early detection of ovarian cancer at earlier stages (Menon et al., 2015) (see Table 3-6). Compared to using different fixed cutoffs for CA-125 concentration, screening with ROCA doubled the number of ovarian or tubal carcinomas detected in the trial. However, as most of the cancer detected at earlier stages was not of the deadly HGSC subtype, this improvement in early diagnosis may not lead to a similarly significant improvement in mortality. Recently published mortality data indicated that there was a 15 percent mortality reduction with CA-125 plus TVU and an 11 percent mortality reduction in TVU alone compared with no screening over 14 years (Jacobs et al., 2015). When the analysis was restricted to years 7 through 14, when most of the mortality occurred, the benefits of the CA-125 and TVU screening were more obvious, as it reduced mortality by 23 percent in this time frame. Although these results are promising, the current methods still need further refining, and it is likely that distinct multimodal approaches will be needed in order to detect each of the various subtypes at their earliest stages.

Japanese Shizuoka Cohort

The Shizuoka Cohort Study of Ovarian Cancer Screening prospective randomized controlled trial involved more than 80,000 asymptomatic postmenopausal women who were enrolled between 1985 and 1999 (Kobayashi et al., 2008). Nearly half of the women were assigned to the intervention arm, which consisted of annual screening with pelvic ultrasound and CA-125 serum measurement. The control arm included no screening. The ultrasound techniques used for the prevalence or first incidence scans were TVU (in the majority of cases screened after 1990) or transabdominal ultrasound. Women with abnormal ultrasound findings or elevated CA-125 levels (or both) were referred for further medical evaluation or investigative surgery by gynecologic oncologists. The trial closed in December 2002 with a mean follow-up period of 9.2 years. A higher proportion of women with Stage I ovarian cancer were identified in the screened group than in the control group, but it was not statistically significant (Kobayashi et al., 2008).

Kentucky Screening Study

Between 1987 and 2005, more than 25,000 women participated in a screening study at the University of Kentucky (van Nagell et al., 2007). In this single-arm study, women received annual TVU screening. The 5-year survival rate in women whose screens were positive and who were diagnosed with invasive ovarian carcinoma was significantly higher than among women treated at the University of Kentucky during the same time period who did not undergo screening (75 versus 54 percent). As improved therapies continue to be developed, even a modest improvement in detection time may improve survival rates.

KEY FINDINGS AND CONCLUSIONS

The committee offers the following findings and conclusions:

- Given the relative rarity of ovarian cancer and the heterogeneity of the disease, consortia are likely to be necessary to achieve the statistical confidence (power) to evaluate risk factor associations by tumor histologic subtype.
- While several risk factors for ovarian cancer have been identified, their associations with specific histologic subtypes require further clarification.
- Not all women who carry germline genetic mutations in cancer-predisposition genes have an apparent family history.

- The contribution that known mutations in the *BRCA1* and *BRCA2* genes, as well as others linked to hereditary cancer syndromes (e.g., Lynch syndome), make to inherited genetic risk is well characterized, yet it does not account for all of the inherited risk for ovarian cancer.
- New mutations identified in recent sequencing studies need further risk quantification before they can be integrated into clinical practice.
- The current understanding of risk factors has limited utility in accurately predicting risk at the individual level; thus, there is a clear need for improved and validated risk prediction models that can be used to screen the general population of women.
- BSO has been shown to drastically reduce a woman's risk of ovarian cancer and is recommended for women known to be at high genetic risk for developing ovarian cancer. Adverse side effects (e.g., surgical complications, loss of fertility, and premature menopause) and the low incidence of ovarian cancer in the general population preclude performance of these surgeries as part of a risk-reducing strategy in women at low or average genetic risk for ovarian cancer.
- The potential impact of opportunistic salpingectomy on reducing risk for women at high risk and average risk of developing ovarian cancer needs to be studied.
- Current imaging technologies for ovarian cancer screening are effective at detecting pelvic masses but are limited in their sensitivity to detect small, early lesions. Efforts to improve early detection through technology are hampered by an incomplete understanding of tumorigenesis, including knowledge about the cell or tissue of origin.
- Current screening methods have not had a substantial impact on overall mortality for general or high-risk populations irrespective of the biomarkers, imaging strategy, or risk prediction algorithms that have been used. In addition, the best currently available protocol for early detection of ovarian cancer (a combination of screening for elevated CA-125 and use of TVU) does not meet the risk–benefit ratio criteria for support by the USPSTF.
- The largest and most recent screening trial, UKCTOCS, has demonstrated a significant improvement in early detection, although the improvement in mortality was modest.
- No reliable biomarker or panel test exists for the detection of early-stage ovarian cancer.

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4

Diagnosis and Treatment

Because of progress over the past few decades, newly diagnosed ovarian cancers are now more accurately and consistently staged than in the past, and, thanks in particularly to better characterization of tumor biology and a personalized medicine approach in therapeutic development, a wider variety of treatment options exist. While this progress is encouraging, there is still much to do, and there are a number of barriers that must be overcome to further improve outcomes for women with ovarian cancers. This chapter discusses the diagnosis and therapeutic management of women with newly diagnosed and recurrent ovarian cancer, discusses new therapies on the horizon, and gives an overview of the cancer clinical trials landscape. As noted in Chapter 1, these discussions focus primarily on the treatment of women diagnosed with high-grade serous carcinomas (HGSCs).

NEWLY DIAGNOSED PATIENTS

Because of the heterogeneity of ovarian cancers, it is essential that the initial diagnosis be accurate. Furthermore, because a variety of benign conditions can mimic ovarian cancer, it is crucial that women with suspected ovarian cancer be carefully examined to help determine the proper clinical management.

Signs and Symptoms

While there are no symptoms specific to ovarian cancer, most women diagnosed with ovarian cancer do experience such things as bloating, pelvic

or abdominal pain, difficulty eating, or urinary symptoms; the problem is that these symptoms are often overlooked until after a diagnosis has already been made. Studies show that 90 percent of women with early-stage ovarian cancer and 100 percent of women with the late-stage disease reported having at least one symptom (Goff et al., 2004; Lataifeh et al., 2005). There is only a marginal difference in the symptoms reported by women with the early-stage disease and those with the late-stage disease (Olsen et al., 2007), and patients and providers do not commonly associate these symptoms with gynecologic issues, which complicates early detection. One way to help raise awareness of the early signs and symptoms of ovarian cancer would be to increase the understanding of these symptoms among providers and then to improve communication between the providers and their patients.

Diagnosis

Several bodies have established guidelines for the initial assessment and treatment of women with suspected ovarian cancer. The Society for Gynecologic Oncologists (SGO), the American College of Obstetricians and Gynecologists (ACOG), and the National Comprehensive Cancer Network (NCCN) have all published guidelines for referral of patients with suspected ovarian cancer (ACOG, 2002; NCCN, 2015) (see Box 4-1). In addition to the difficulties created by the vagueness of the symptoms described above, it can be challenging to make an accurate diagnosis of ovarian cancer in women with widespread disease because gastrointestinal tumors can mimic an ovarian cancer at initial presentation (Munoz et al., 2012). In the clinic, a woman most often presents with carcinomatosis-associated ascites, and a diagnosis is often made by paracentesis with cytologic review of ascites, fine needle aspiration, or laparoscopic biopsy.

Pathological and Surgical Reporting

Complete and detailed pathological and surgical reporting is necessary for both the characterization of the disease and the determination of the treatment course. In general, the first step is to perform a tumor biopsy or primary debulking surgery (PDS). (See next section in the chapter for more on PDS.) Important information to collect in surgical operative reports includes an accurate description of the biopsy sites and an objective description and documentation of the extent of residual disease (Robboy et al., 2002). The collected tissues are used for pathological evaluation. The College of American Pathologists Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary lists the following crucial components for all pathology reports:

BOX 4-1
Ovarian Cancer Assessment Guidelines Summary

Clinical presentation

1. Detection of pelvic mass on exam
2. Symptoms: e.g., bloating, pelvic or abdominal pain, early satiety, urinary symptoms
3. Concern raised on screening assays (e.g., CA-125)
4. Incidental findings on previous surgery or tissue biopsy

Workup

- Family history of breast or ovarian cancer
- Abdominal/pelvic exam
- Imaging: chest, abdominal, and pelvic CT/MRI as indicated
- Blood tests: CBC, chemistry profile, liver function tests; CA-125 and other serum biomarkers (e.g., inhibin, AFP, beta-HCG) as indicated
- Needle aspiration should be avoided for diagnosis in patients with presumed early-stage disease to prevent tumor rupture and spread

NOTE: AFP = alpha-fetoprotein; CA-125 = cancer antigen 125; CBC = complete blood count; CT = computed tomography; HCG = human chorionic gonadotropin; MRI = magnetic resonance imaging.
SOURCES: ACOG, 2002; NCCN, 2015.

- Specimen integrity;
- Histology;
- Tumor grade (particularly for serous tumors); and
- Tumor stage (extent of involvement of other tissues/organs in a systematic manner) (Scully et al., 1996).

The accuracy of these records is crucial in ensuring effective patient care because many treatment decisions are based in large part on these reports. However, traditional operative and pathology reports frequently do not capture these important data (Donahoe et al., 2012; Gogoi et al., 2012). In one study, up to 25 percent of all operative reports lacked documentation of residual disease for ovarian cancer patients (Gogoi et al., 2012). Another evaluation of nearly 500 pathology reports for advanced ovarian, fallopian tube, and primary peritoneal cancers found that although most specimens were microscopically described (92.3 percent of reports), tumor size or weight was missing in 40.1 percent of reports, and, a description of the tumor origin was missing in 20.5 percent of surgical reports for PDS and 23.4 percent of surgical reports for interval debulking procedures (Verleye et al., 2011).

Once a diagnosis of ovarian cancer has been confirmed by pathological evaluation, patients with newly diagnosed ovarian cancer are generally managed with a combination of surgery and chemotherapy.

Surgical Management

The key goals for surgical intervention in women with suspected ovarian cancer include establishing the initial diagnosis, determining the extent of disease spread (staging), and deciding on the best course of therapy. Accurate staging is particularly relevant in those cases where the disease appears to be confined to the ovary, because the subsequent therapeutic course is largely prescribed according to tumor stage (Winter-Roach et al., 2012) (see Box 4-2 for staging criteria).

For women with early-stage (Stage I or II) ovarian cancer, complete surgical staging is also an important prognostic indicator (NIH Consensus Development Panel on Ovarian Cancer, 1995). For example, in a study of women with Stage I ovarian carcinoma who had received a lymphadenectomy (the surgical removal of one or more groups of lymph nodes), nearly 7 percent

BOX 4-2
International Federation of Gynecology and Obstetrics (FIGO)

Staging Criteria for Ovarian Cancer

Stage I: Tumor confined to one or both ovaries or fallopian tubes
- IA. Tumor limited to one ovary (capsule intact) or fallopian tube
- IB. Tumor limited to both ovaries or fallopian tubes
- IC. Tumor limited to both ovaries or fallopian tubes with any of the following:
  - IC1. Surgical spill intraoperatively
  - IC2. Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
  - IC3. Malignant cells present in the ascites or peritoneal washings

Stage II: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
- IIA. Extension and/or implants on any one or more of the following: uterus, fallopian tube(s), ovaries
- IIB. Extension to other pelvic intraperitoneal (IP) tissues

Stage III: Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically and histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

of the women had greater disease-specific survival (Chan et al., 2007a). In the absence of complete staging, the full extent of residual disease may be unknown, which could affect decisions about the treatment course. Given the necessity for a sophisticated diagnostic and initial surgical approach, evidence shows that the surgical treatment for ovarian cancers is best performed by those with expertise in managing this disease specifically (e.g., gynecologic oncologists) (Giede et al., 2005; Hacker, 2011; Vernooij et al., 2007).

For women newly diagnosed with ovarian cancer, the amount of tumor remaining after PDS is among the most important prognostic factors for both progression-free survival (PFS) and overall survival (Bristow et al., 2002; du Bois et al., 2009; Eisenkop et al., 1998; Elattar et al., 2011; Griffiths, 1975; Hoskins et al., 1994). The goal of PDS is always to achieve a complete resection of the tumor. Several factors affect whether a patient experiences complete resection (no residual tumor), optimal cytoreduction (residual tumor ≤ 10 mm in diameter), or suboptimal cytoreduction (residual tumor > 10 mm in diameter) (Chi et al., 2012; du Bois et al., 2009; Hacker, 2013). These factors include the size of the tumor at diagnosis (as indicated by FIGO stage) and the aggressiveness of the surgical practice.

IIIA. Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
- IIIA1. Positive retroperitoneal lymph nodes only (cytologically or histologically proven)
  - IIIA1(i). Metastasis ≤ 10 mm in greatest dimension (note that this is a tumor dimension and not a lymph node dimension)
  - IIIA1(ii). Metastasis > 10 mm in greatest dimension
- IIIA2. Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

IIIB. Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

IIIC. Macroscopic peritoneal metastases beyond the pelvic brim > 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes

Stage IV: Distant metastasis excluding peritoneal metastases
- IVA. Pleural effusion with positive cytology
- IVB. Metastases to extra-abdominal organs

SOURCE: Mutch and Prat, 2014.

A study of nearly 1,300 women with ovarian carcinoma enrolled in three Phase III randomized trials testing different chemotherapy regimens found that both PFS and overall survival differed significantly for women who had complete resection (i.e., no residual tumor) versus those who had either optimal cytoreduction or suboptimal cytoreduction (du Bois et al., 2009). Overall survival differences were more pronounced for patients with Stage II (a 46-month improvement) or Stage III (a 60-month improvement) disease but were still significant for patients with Stage IV disease (average 30-month improvement).

In addition to women who have had suboptimal cytoreduction, there are women who are unable to undergo PDS at all because of the presence of comorbidities that preclude initial surgery. For these women, neoadjuvant chemotherapy (NACT) is used to reduce the tumor burden (the amount of cancer or the size of the tumor) and facilitate subsequent surgical resection (Morrison et al., 2012; Vergote et al., 2013). Increasingly, advanced-stage ovarian cancer patients with extensive metastasis (noted on imaging studies or at the time of diagnostic laparoscopy) are being managed with three to four cycles of NACT prior to an interval cytoreduction. Results from two separate trials suggested that patients who have undergone NACT have similar PFS and overall survival rates to patients who have undergone PDS (Kehoe et al., 2015; Vergote et al., 2010). However, these findings were met with skepticism from several groups in the gynecologic oncology community who criticized various elements of the trial design (Dai-yuan et al., 2013; du Bois et al., 2012; Gasparri et al., 2015; Hacker, 2013; Kehoe and Nankivell, 2015; Scaletta et al., 2015; Vergote et al., 2013). As such, the question of which women should receive initial PDS or NACT remains unresolved. The prognostic role of other endpoints—such as pathologic complete response, which is commonly utilized in NACT studies in breast cancer—may provide additional details in NACT studies in ovarian cancer. Nonetheless, NCCN guidelines do allow for the consideration (based on category 1 evidence) of NACT for patients with bulky Stage III to IV disease if maximum cytoreduction cannot be achieved (NCCN, 2015). Evidence suggests that a number of disease characteristics (e.g., tumor volume and stage) and patient characteristics (e.g., age at diagnosis) are significantly associated with outcome after PDS or NACT and need to be considered when evaluating patients (Horowitz et al., 2015).

Several prognostic and predictive biomarkers are currently used to determine whether other types of cancer patients will benefit from particular targeted therapies. These include HER2/Neu protein amplification for Herceptin® use against breast tumors, and epidermal growth factor receptor (EGFR) protein amplification for anti-EGFR therapeutics, which are used against a wide variety of tumors, including ovarian tumors (Baselga, 2006; Grunwald and Hidalgo, 2003; Yeon and Pegram, 2005). Although these

targeted therapies may not work in all ovarian cancers, HER2-positive mucinous carcinomas may be a viable target for anti-HER2 therapies (Anglesio et al., 2013; Teplinsky and Muggia, 2015). As discussed in Chapter 3, the protein biomarker cancer antigen 125 (CA-125) has been studied as a predictive biomarker for ovarian cancer risk, though its primary use is to monitor tumor progression. It has also been investigated for other uses, including predicting tumor response to chemotherapy and the probability of PFS and overall survival. It has been suggested that biomarkers such as CA-125 and human epididymis protein 4 (HE-4) can play a role in aiding clinical decision making for initial PDS or NACT (Nolen and Lokshin, 2013).

Chemotherapy Management

The earliest use of chemotherapy for the treatment of advanced ovarian cancer involved the intravenous (IV) delivery of doxorubicin (an anthracycline) and cyclophosphamide (a DNA cross-linking agent). These chemicals are cytotoxic, meaning that they kill cells, especially cancer cells. In the 1980s, the platinum-based agent cisplatin was shown to significantly improve response rates and survival when added to the protocol (Neijt et al., 1984; Omura et al., 1986). Later trials found little difference in clinical efficacy between the two-drug combination of cisplatin and cyclophosphamide and multidrug combinations including anthracyclines, so the combination of cisplatin and cyclophosphamide became standard chemotherapy for the first-line treatment of advanced ovarian cancer (Bertelsen et al., 1987; Omura et al., 1989).

In 1994, the first National Institutes of Health (NIH) Consensus Conference on Ovarian Cancer released recommendations for the chemotherapeutic management of newly diagnosed or post-operative ovarian cancer (NIH Consensus Development Panel on Ovarian Cancer, 1995). Based on the results of chemotherapy trials that had been conducted in the previous decade, the conference recommended that all women diagnosed with Stage IC–IV ovarian cancer receive adjuvant chemotherapy following PDS. (Women with Stage IA or IB ovarian cancer were only recommended to have surgery.) Since then, subsequent trials (see Table 4-1) using different treatment protocols for first-line and maintenance therapy have led to further improvements in PFS and in overall survival (Burger et al., 2011; du Bois et al., 2003; Katsumata et al., 2009; McGuire et al., 1996; Ozols et al., 2003; Perren et al., 2011; Piccart et al., 2000).

The current standard of care is a platinum-based chemotherapeutic agent (e.g., cisplatin or carboplatin), which may be given in combination with taxane agents (e.g., paclitaxel) (NCCN, 2015). Carboplatin administered every 3 weeks in combination with paclitaxel administered every 3 weeks or every week (dose dense) is now the standard treatment for ovar-

TABLE 4-1
Clinical Trials of Intravenous Chemotherapy Protocols for Ovarian Cancer

Therapy	Trial(s)	Treatment Changes	References
Front line	GOG-111, OV10	Replacement of IV cyclophosphamide with IV paclitaxel in combination with IV cisplatin	McGuire et al., 1996; Piccart et al., 2000
	AGO OVAR-3, GOG-158	Replacement of IV cisplatin with IV carboplatin in combination with paclitaxel	du Bois et al., 2003; Ozols et al., 2003
	NCT00226915	Dose-dense IV paclitaxel (80 mg/m^2 weekly) in combination with standard IV carboplatin	Katsumata et al., 2009
	GOG-217, ICON 7	Addition of bevacizumab to IV paclitaxel and IV carboplatin	Burger et al., 2011; Perren et al., 2011
Maintenance	GOG-178	Additional 12 months of paclitaxel	Markman et al., 2003

ian cancer patients who have suboptimal cytoreduction or who are treated with NACT. For patients with advanced-stage ovarian cancer who have undergone optimal cytoreduction, intraperitoneal (IP) chemotherapy has proven to be one of the more effective treatment strategies.

Intraperitoneal Chemotherapy

For both primary and metastatic ovarian cancers, the peritoneal cavity is the principal site of disease upon diagnosis (Lengyel, 2010). Several routes exist for delivering chemotherapy that will reach that site: through an IV line, orally (by mouth), and through an implanted IP catheter.

In the 1950s, IP chemotherapy was used for patients with malignant pleural, peritoneal, or pericardial effusions from several types of primary cancer (Weisberger et al., 1955). In delivering pharmaceutical agents for the treatment of ovarian carcinoma, the method that consistently led to the highest concentrations of the drug in ascites was the IP route (Ward et al., 1987). Subsequent studies have confirmed that IP delivery results in an increased drug concentration at the tumor site and have indicated that IP delivery also results in fewer adverse systemic side effects than IV or oral routes (Jaaback et al., 2011). However, IV and oral chemotherapy are the most common modes of treatment for ovarian cancer in general, while fewer than half of patients with ovarian carcinoma receive IP chemotherapy in addition to IV chemotherapy (Wright et al., 2015).

In the past two decades, several clinical trials have tested different combinations and doses of IP chemotherapy agents, including three trials that had not yet released results as this report was being written (Alberts et al., 1996; Armstrong et al., 2006; Mackay et al., 2011; Markman et al., 2001). While these trials have had variable results, they all have shown that combined IV and IP chemotherapy administration improves survival in women with Stage III, optimally resected disease compared with standard IV administration alone (Hess et al., 2007; Jaaback et al., 2011). The seminal results from the 2006 GOG-172 clinical trial showed that treatment with IP chemotherapy resulted in a 5-month improvement in median PFS and a 16-month improvement in median overall survival over IV chemotherapy (Armstrong et al., 2006). A subsequent long-term follow-up found a nearly 10-month increase in median survival and a 23 percent decreased risk of death for patients treated with the IP protocols compared with IV protocols, suggesting a sustained benefit from IP chemotherapy (Tewari et al., 2015).

However, tumor histology may play a role in how well a patient responds to IP chemotherapy, so that not all women with ovarian cancer benefit equally from IP chemotherapy. Among patients with aberrant *BRCA1* gene expression, those treated with IP chemotherapy had a significantly better median overall survival (84 months) than those treated using only IV chemotherapy (47 months), but no significant difference was seen among patients with normal *BRCA1* expression (Lesnock et al., 2013). Among the various subtypes of ovarian cancer, the advantage of IP over IV chemotherapy is most pronounced for serous tumors, but only if all six cycles of therapy are delivered.

The adoption of IP chemotherapy protocols is not yet widespread among clinicians because of concerns about some potential serious adverse effects of IP administration, including drug-related toxicities, complications from catheter use, delivery of chemotherapy beyond the peritoneum, and poor tolerance of the treatment (Wright et al., 2015). Another concern is that the delivery of IP chemotherapy is sometimes inconsistent (e.g., the full six cycles of intended therapy are not always completed). Furthermore, among hospitals that have adopted IP chemotherapy into the standard of care, there appears to be great variation in the number and types of patients who receive it (Wright et al., 2015). The delivery of dose-dense paclitaxel, a newer IV dosing regimen, has demonstrated similar efficacy to the IP protocols without many of the accompanying toxicities (Katsumata et al., 2009). However, questions remain concerning direct comparisons between IP chemotherapy regimens and the equivalent doses and schedules that are administered via the IV route. Three large-scale trials are currently examining carboplatin-based IP chemotherapy:

- iPocc Trial (GOTIC-001/JGOG-3019);
- GOG-252; and
- OV-21/CGIG.

Although these trials have different patient populations and different treatment regimens, they will help answer important questions regarding the administration and comparative effectiveness of IP versus IV chemotherapy.

Maintenance Therapy

Maintenance therapies may be beneficial for women with advanced ovarian cancers, especially given the high rates of recurrence with standard therapies. Several trials have tested a variety of agents for use in maintenance therapy, including hormones, radiation, chemotherapy, immunotherapy, biological therapy, and complementary medicines. At its interim analysis, GOG-178, a Phase III trial, found that 12 additional months of paclitaxel provided a 7-month improvement in PFS, and the study was closed to further accrual (Markman et al., 2003). GOG-212 is a Phase III confirmatory trial that has completed accrual and will provide further guidance regarding the role of cytotoxic chemotherapy agents as a maintenance strategy in ovarian cancer.

Within the past decade, several randomized studies have investigated the various roles of anti-angiogenic agents (e.g., bevacizumab, pazopanib, and cediranib) and poly ADP ribose polymerase (PARP) inhibitors (e.g., olaparib) as a maintenance strategy in patients with advanced or relapsed ovarian cancers. Trials have demonstrated an improvement in PFS with the use of bevacizumab as a maintenance regimen (after primary chemotherapy). Trials investigating PARP inhibitors alone and in combination with chemotherapy have likewise demonstrated improvement in PFS and have led to U.S. Food and Drug Administration (FDA) approval of olaparib as a monotherapy for ovarian cancer patients with a *BRCA* mutation who have received three prior chemotherapy regimens (Kaye et al., 2012; Kim et al., 2015; Ledermann et al., 2012). Additional trials are now in progress to investigate several other anti-angiogenic agents and PARP inhibitors as maintenance options. For instance, SOLO2 is investigating maintenance treatment with olaparib, with results expected in 2016. The FDA did not support an accelerated approval of olaparib and stated that its decision on whether to approve olaparib for maintenance therapy needed to be delayed until the final results were available (FDA, 2014c). Some of the issues that the FDA was concerned about were the validity of the effects, the trial's statistical analysis, and potential risks associated with the drug. In addition, questions remain regarding which endpoints may be necessary to accurately capture the effects of maintenance therapy in ovarian cancer (Ledermann

and El-Khouly, 2015). It may be necessary to explore additional clinical trial endpoints in order to adequately assess maintenance therapy and ensure that patients do indeed benefit from this treatment.

RECURRENT OVARIAN CANCER

Despite the high response rate to aggressive initial treatments, most women diagnosed with advanced ovarian cancer will eventually have a recurrence (Coleman et al., 2013). The rate of relapse in ovarian cancers is highly dependent on the initial stage at diagnosis, the histologic type, and the presence of residual disease at the time of primary or interval debulking. Women with Type II ovarian cancers (e.g., HGSC) are also likely to have higher rates of recurrence.

Several organizations have established guidelines for monitoring women for recurrence (Salani et al., 2011). Although many women with recurrent ovarian cancer will be symptomatic or have detectable signs of recurrence upon physical examination, an increasing number of women are being (or could be) diagnosed with recurrent ovarian cancer through the detection of incremental rises in CA-125 and through the use of more sophisticated imaging technology (Bhosale et al., 2010; Prat et al., 2009). Diagnosing recurrent ovarian cancer earlier may improve physicians' ability to achieve maximum secondary cytoreduction. However, there are limited data to suggest that an earlier diagnosis of recurrence improves overall survival, and, indeed, it may instead lead to interventions that negatively affect the patient's quality of life (Clarke et al., 2014; Fleming et al., 2011; Rustin et al., 2010). Some argue that following up with CA-125 testing after primary therapy may be unneccesary and that its use should be discouraged (Rustin, 2011). Additional studies may be needed to examine the various follow-up methods and assess whether early intervention improves survival or quality of life, especially as new treatments for relapsed ovarian cancer become available. Additional considerations such as the distress and other psychosocial effects caused by continued monitoring for recurrence need to be considered when evaluating the effectiveness of surveillance (Parker et al., 2006). (For more on supportive care for the physicial and psychosocial effects of diagnosis and treatment, see Chapter 5.)

Patients with recurrent ovarian cancers have traditionally been categorized as either platinum sensitive (if recurrence is diagnosed more than 6 months after prior therapy) or platinum resistant (if recurrence is diagnosed less than 6 months after prior therapy). However, it may be time to consider developing a new classification paradigm for recurrent ovarian cancers, particularly given the ability to diagnose these recurrences at earlier time points, the increased understanding of the impact that *BRCA* mutation status has on a patient's response to therapy for recurrence, and the hetero-

geneous responses noted in patients who are classified as platinum resistant (Davis et al., 2014; Guth et al., 2010).

Surgical Management

Like newly diagnosed women, women with recurrent ovarian cancer have improved outcomes when there is a complete resection of the cancer (Al Rawahi et al., 2013; Harter et al., 2006). There are several ongoing trials evaluating secondary cytoreduction in patients with recurrent ovarian cancer, two of which have overall survival as the primary endpoint (van de Laar et al., 2014). Secondary (and further) cytoreduction is generally reserved for patients with isolated, resectable, platinum-sensitive disease. Validated scoring systems can be used to predict which women with recurrent ovarian cancers undergoing secondary cytoreduction are most likely to achieve complete resection of all visible disease (Harter et al., 2011, 2014; Nick et al., 2015; Tian et al., 2012; Wimberger et al., 2007). Limited studies of tertiary (and beyond) cytoreduction in patients with recurrent ovarian cancer that suggest complete resection is feasible, and this remains the most important factor in predicting a patient's survival (Fotopoulou et al., 2011, 2013; Liu et al., 2014b).

Chemotherapy Management

Once ovarian cancer recurs, the appropriate chemotherapy strategy will depend on the length of time to relapse (Friedlander et al., 2011; Stuart et al., 2011). Several trials have found better outcomes with carboplatin-based combination cytotoxic chemotherapies than for single-agent carboplatin for patients with platinum-sensitive recurrent ovarian cancers (Parmar et al., 2003; Pfisterer et al., 2006; Raja et al., 2013; Wagner et al., 2012). Patients with cancers that are not responsive to front-line therapy are typically treated with other agents (e.g., liposomal doxorubicin, gemcitabine, topotecan, or etoposide), but the overall response to these agents remains poor (less than 20 percent) and the median PFS is only 3 months on average (Agarwal and Kaye, 2003; Luvero et al., 2014). A better understanding of the genetic differences between the initial ovarian cancer cells and the drug-resistant ovarian cancer cells could help direct efforts to design targeted therapies.

Two new agents have recently been approved by the FDA for patients with recurrent ovarian cancer. Bevacizumab, a humanized antibody that blocks vascular endothelial growth factor (VEGF), in combination with one of three chemotherapy regimens (i.e., dose-dense paclitaxel, liposomal doxorubicin, and topotecan), is now approved for the treatment of patients with platinum-resistant ovarian cancers. Olaparib, a PARP inhibitor, has

been approved as a monotherapy for *BRCA* mutation–positive, recurrent ovarian cancer patients who have had three prior chemotherapy treatments.

Evaluating Chemosensitivity and Chemoresistance

Understanding which tumors are likely to be resistant to chemotherapeutic agents after recurrence is a key step in improving overall survival. Several assays have been developed (or are in development) for determining the likelihood that primary and relapsed tumors will respond to various chemotherapeutic agents (Rutherford et al., 2013). There is some evidence to suggest that sensitivity to platinum agents differs by tumor histologic subtype, with Type I tumors showing greater sensitivity than Type II tumors (Berns and Bowtell, 2012; Gershenson, 2012; Kobel et al., 2008; Storey et al., 2008; Vang et al., 2009). This heterogeneity complicates assay development efforts in which tumor samples must be divided into small subsets in order to more accurately determine therapy efficacy.

No systematic review supports the role of chemosensitivity assay–directed care for patients with recurrent ovarian cancer. Similarly, molecular profiling for the identification of potential molecular targeted therapies for patients with recurrent ovarian cancer, while feasible, has not been demonstrated to be associated with improved outcomes (Kohn, 2014; Plamadeala et al., 2015; Rutherford et al., 2013). New clinical trials, such as the National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH), seek to analyze patient tumors for genetic abnormalities in order to determine if a targeted drug exists for use in treatment (NCI, 2015). Some of the targeted therapies in this trial may be effective in treating ovarian cancer.

THE DELIVERY OF OVARIAN CANCER CARE

The Institute of Medicine (IOM) reports *Ensuring Quality Cancer Care* and *Delivering High-Quality Cancer Care* looked at the delivery of cancer care overall (IOM and NRC, 1999; IOM, 2013) and offered a variety of findings and conclusions. The 2013 report found that "cancer care is often not as patient-centered, accessible, coordinated, or evidence-based as it could be" (IOM, 2013, p. 2). The growing demand for care (mostly due to the aging population), a shrinking workforce, and rising costs are issues that affect the care of patients with many types of cancer (and other serious diseases). Furthermore, "in the current cancer care system, many patients lack access to affordable, high-quality cancer care" (IOM, 2013, p. 309). Clinical trials in cancer care tend to have lower levels of enrollment among older adults and racial and ethnic minorities (Lewis et al., 2003; Murthy et al., 2004; Stewart et al., 2007; Talarico et al., 2004). There are major

disparities in cancer outcomes that negatively affect individuals who are of lower socioeconomic status, are racial or ethnic minorities, or who are underinsured or lack health insurance coverage (IOM, 2013). Furthermore, a focus on the delivery of treatment for the disease often overshadows consideration for the patient's preferences and their supportive care needs, including the treatment and management of the physical and psychosocial effects of diagnosis and treatment (see Chapter 5). A review of the literature on the delivery of cancer care (or the challenges in the health care system in general that affect cancer care) is beyond the scope of this report, but the following sections highlight the overarching findings in the research of cancer care delivery and discuss the specific evidence related to the delivery of care for women with ovarian cancer.

Standard-of-Care Guidelines

According to the 2013 IOM report, "clinical research leads to improvements in the quality of care only if these research results are translated into clinical practice" (IOM, 2013, p. 293). Professional societies and organizations help to develop standard-of-care guidelines based on currently available data. Women with ovarian cancer who receive care in accordance with NCCN clinical practice guidelines have considerably better clinical outcomes (e.g., improved survival and fewer surgical complications) (Bristow et al., 2013b; Chan et al., 2007b; Eisenkop, et al., 1992; Goff, 2015). However, 56 percent of women with ovarian cancer nationwide do not receive care that adheres to these guidelines (Cliby et al., 2015). Furthermore, as was discussed in Chapter 3, the percentage of women who are referred to genetic counseling and testing in accordance with existing guidelines is low, and nearly half of all eligible women are not receiving recommended counseling (Febbraro et al., 2015; HHS, 2013; Powell et al., 2013). (See Table 3-3 for current recommendations for cancer genetic consultation and germline genetic testing for women with a personal or family history of ovarian cancer.)

The most significant predictors of whether women will receive the standard of care are whether they are treated by a gynecologic oncologist (as compared to a general gynecologist or general surgeon) and whether they are treated in a high-volume (often urban) or a low-volume (often rural) hospital or cancer center; treatment by a gynecologic oncologist and in a high-volume setting are associated with better outcomes (Bristow et al., 2013a, 2014). Significant predictors of nonadherence to the standard of care include advanced age at diagnosis, the presence of one or more treatment-limiting comorbidities, non-white race, and lower socioeconomic status (Bristow et al., 2013a,b; Chase et al., 2012; Du et al., 2008; Erickson et al., 2014; Goff et al., 2007; Harlan et al., 2003; Howell et al., 2013;

Jordan et al., 2013; Joslin et al., 2014; Thrall, 2011). Some studies have found a geographic variation in the patterns of cancer care, which may be due to socioeconomic or other factors (Fairfield et al., 2010; Polsky et al., 2006; Ulanday et al., 2014).

Individual Patient Considerations

A physician developing a treatment plan for a woman with ovarian cancer needs to consider not only the disease diagnosis itself, but also other factors related to demographics and patient preferences.

Caring for Older Adults

The 2013 IOM report noted that "the population of those 65 years and older comprises the majority of patients who are diagnosed with cancer and who die from cancer, as well as the majority of cancer survivors" (IOM, 2013, p. 2). Similarly, most ovarian cancers are diagnosed in older women (see Chapter 1). The care for older adults with cancer in general can be affected by alterations in their physiology and by their functional impairments, comorbidities, and treatment goals (IOM, 2013). Some of the areas that have been identified as in need of further research in general for the cancer care of older adults include the efficacy and toxicity of commonly used therapeies in older patients, clinical trials to better understand specific issues for older patients (including consideration of comorbidities), and the outcome measures that are most important for older adults (Hurria et al., 2012; Moy et al., 2014). NRG Oncology and the NCI are collaborating on an open observational trial to study "comprehensive patient questionnaires in predicting complications in older patients with gynecologic cancer undergoing surgery. Comprehensive patient questionnaires completed before surgery may help identify complications, such as the need for assistance in taking medications, decreased mobility, decreased social activity, and falls, and may improve outcomes for older patients with gynecologic cancer" (NRG Oncology, 2015).

As noted above, older women with ovarian cancer are less likely to be treated by a gynecologic oncologist and are less likely to receive care in accordance with standard-of-care guidelines. For example, one study of women with advanced ovarian carcinoma showed that only 39.1 percent of women older than age 65 had surgery and at least six cycles of chemotherapy (Thrall et al., 2011). Given that ovarian cancer is largely a disease of older women, more research is needed on the issues that are particularly relevant for the care of older women with ovarian cancer, including differing preferences, treatment goals, and supportive care needs along the survivorship trajectory (see Chapter 5).

Obesity

Obesity is a growing challenge in the treatment of cancer in general. Obesity complicates treatment by creating challenges in determining the correct dosage for chemotherapy, in performing surgery (e.g., airway complications), and in administering radiation therapy (Calle et al., 2003; Griggs et al., 2012; Sparreboom et al., 2007; Washam, 2012; Welsh et al., 2011). Obesity creates similar challenges in the treatment of gynecologic cancers (Blikkendaal et al., 2015; Modesitt and van Nagell, 2005). Poor nutrition, sedentary lifestyle, and obesity have been associated with a lower quality of life and survival rates among women with ovarian cancer (Nagle et al., 2015; Pavelka et al., 2006; Smits et al., 2015a; Torres et al., 2013). (See Chapter 5 for more on survivorship issues related to diet and exercise.) However, one study did find that survival rates were similar between obese and non-obese women when optimal debulking surgery was performed in both sets of patients (Matthews et al., 2009), and another showed that obesity was associated with wound complications and prolonged hospital stay, but not with cytoreduction status or 30-day mortality (Smits et al., 2015b). Therefore, more research is needed both on how to adjust treatment approaches for obese women and also on how to incorporate weight and nutrition counseling into the treatment plan.

Patient Engagement

The 2013 IOM report stated, "A high-quality cancer care delivery system depends upon clinical research that gathers evidence of the benefits and harms of various treatment options so that patients, in consultation with their clinicians, can make treatment decisions that are consistent with their needs, values, and preferences" (IOM, 2013, p. 207). However, the report found that patient-centered communication and shared decision making in oncology is "suboptimal," with clinicians asking for patient preferences in medical decisions only about half the of the time (IOM, 2013). The patient's voice is often lost when clinicians are developing treatment plans for women with ovarian cancer, and more needs to be done to ensure better communication between women and their care providers when developing such plans. (See Chapter 5 for more on patient preferences, shared decision making, and patient–provider communication.)

The possibilities for patient engagement go beyond simply tailoring treatment plans to take patient preferences into account. In practice, all types of patients play a role in their own care teams, and they can contribute to their own care in a variety of ways. One example is the use of patient-reported outcomes (PROs) to help inform the care team. PROs can facilitate the systematic assessment of disease- and treatment-related

symptoms and impairments in quality of life in both clinical and research settings, but these data are often underreported. (See Chapter 5 for more on patient-reported outcomes.) Researchers should consider using endpoints in clinical trials that better reflect the outcomes of greatest importance to women with ovarian cancer (e.g., quality of life versus overall survival). Furthermore, more research is needed into the issue of how better to include the collection and validation of PROs in the health care delivery system. For example, various technologies, such as wearable sensors, and real-time data may be useful in improving both patient self-management and provider assessment and monitoring (Appelboom et al., 2014; Cereda et al., 2007; Dobkin and Dorsch, 2011).

Access to Care

The previous IOM reports on cancer care identified several factors that affect access to cancer care, including

- Health insurance coverage;
- Affordability of care (e.g., cost of care, reduction in work productivity, and transportation);
- Health care delivery system attributes (e.g., geographic distribution of facilities);
- Patient attributes (e.g., health literacy, language, or cultural factors); and
- Clinician attributes (e.g., communication style and cultural competency) (IOM and NRC, 1999; IOM, 2013).

For women with ovarian cancer, receiving care in cancer centers that have experience in treating ovarian cancer (i.e., high-volume centers) or from gynecologic oncologists is associated with an increased likelihood of receiving the standard of care and with better outcomes, but getting access to such care can be a challenge (Bristow et al., 2009, 2014; Cliby et al., 2015). A recent study found that two-thirds of all centers providing initial management of ovarian cancer treat one to seven cases annually (Cliby et al., 2015). The limited research that has been done with women with ovarian cancer has found disparities in access to high-volume cancer centers, with women from racial and ethnic minority groups, women with low socioeconomic status, and women on Medicaid being less likely to have access to these centers (Aranda et al., 2008; Bristow et al., 2014). One study showed that women treated in public hospitals in New York City were less likely to have surgery by a gynecologic oncologist and less likely to have a surgeon who treated a high volume of ovarian cancer cases (Boyd et al., 2011). Tele-oncology may be one way to provide improved access to care to

women in rural areas or at centers without gynecologic oncologic specialists (Shalowitz et al., 2015). Other models of care will need to be developed and assessed for their ability to improve access to the standard of care.

Women with ovarian cancer also experience challenges in accessing recommended genetic counseling and testing (see Chapter 3). There are various patient-, provider-, and system-level barriers that hinder cancer genetics referrals, including patients being unaware that they have a family history of cancer, the limited time that providers have to collect family histories, and complex and non-standardized referral criteria (Hampel et al., 2015). Again, it will be necessary to develop and assess new models of care and new methods for delivering necessary information (e.g., the use of video) to patients.

Finally, women with ovarian cancer may not receive the appropriate standard of care when being treated for ovarian cancer because of insurance coverage policies that preclude them from going to particular providers (e.g., gynecologic oncologists and high-volume cancer centers) or that preclude payment for certain genetic tests.

Health Care Workforce

The 2013 IOM report *Delivering High-Quality Cancer Care* noted that "the cancer care team includes those with specialized training in oncology, such as oncologists and oncology nurses, other specialists and primary care clinicians, as well as family caregivers and direct care workers" (IOM, 2013, p. 153). The report pointed to the need for adequate numbers of health care clinicians with training in oncology and for new models of interprofessional, team-based care. The delivery of care in accordance with the standard of care in part depends on the number of qualified and available members of the cancer care team, the capacity to adequately train a qualified (and larger) cancer care workforce, and the ability to pay for specialty care (e.g., genetic counseling) (IOM, 2009, 2013).

Research has shown that women with ovarian cancer who are provided treatment (e.g., assessment and cytoreductive surgery) by a gynecologic oncologist have longer survival times than women treated by a general gynecologist or general surgeon (Bristow et al., 2009, 2013b; Chan et al., 2007b; Eisenkop et al., 1992). Furthermore, NCCN guidelines recommend that surgery on an ovarian carcinoma be carried out by a gynecologic oncologist (NCCN, 2015). One study has also shown that while the use of gynecologic oncologists did not vary across racial and ethnic groups, women older than 70 were less likely than younger women to receive care from a gynecologic oncologist (Austin et al., 2013). Little evidence exists on the level and types of training that health care professionals other than gynecologic oncologists receive in caring for women with ovarian cancer.

Given that most cancers are diagnosed in older adults, enhancing the geriatrics competence of cancer care teams may be important (IOM, 2008, 2013). Consultation with clinicians with expertise in geriatrics may also be warranted (Girre et al, 2008; Schiphorst et al., 2015). The 2013 IOM report recommended that "members of the cancer care team should coordinate with each other and with primary/geriatrics and specialist care teams to implement patients' care plans and deliver comprehensive, efficient, and patient-centered care" (IOM, 2013, p. 10). Furthermore, as noted above, patient–provider communication about patient preferences is often lacking. In part, this is due to "clinicians' lack of training in communication and insensitivity to patients' informational, cultural, and emotional needs" (IOM, 2013, p. 102). Given this situation, more consideration may be needed for the use of other health care professionals (e.g., nurses and social workers) or the use of technology (e.g., mobile health technologies) in innovative interdisciplinary models of care so that patient–provider communication between women and their care teams is enhanced and the delivery of important information is improved.

While family caregivers provide much needed care and support in general, they are often neglected as an important part of the health care workforce. For older adults, family and friends often play such roles as helping make treatment decisions, accompanying patients on health care visits, providing assistance with daily actitivies, and even providing an increasingly complex level of medical care within the home (IOM, 2008). In 2013, the IOM noted that family caregivers are "particularly important in cancer care because of the debilitating effect of the disease; the side effects associated with many of the common cancer treatments; the complexity of the medical decisions; and the ongoing need for medical treatment, home care, and surveillance" (IOM, 2013, p. 183). Little research has been done specifically on family caregivers for women with ovarian cancer, but one study showed that these caregivers express concerns about a lack of support from the health care community in addressing disease-specific needs and also express a need to connect with others in similar situations (Ferrell et al., 2002).

As noted above, patients themselves also play a sizeable role on their own care team. As the 2008 IOM report noted, "Patients play a major part in determining treatment plans, navigating the delivery system to obtain services, and ensuring overall adherence to the selected course of treatment. For older adults, these care plans often involve multiple providers and settings, and they can find themselves functioning as coordinators of the entire process" (IOM, 2008, p. 241). Chapter 5 provides a more detailed discussion on the role for women with ovarian cancer in helping to determine and manage their treatment plan and course, particularly through the use of shared decision making, self-management, and PROs.

Cancer Quality Metrics

Cancer quality metrics "serve a number of roles in assessing quality of care by providing a standardized and objective means of measurement" (IOM, 2013, p. 272). Several organizations (e.g., the National Quality Forum, the Agency for Healthcare Research and Quality, the American Society for Clinical Oncology, and the American College of Surgeons' Commission on Cancer Care have developed or endorsed quality measures for cancer care (or measures that can be applied to cancer care) (IOM, 2013). Such measures can be used for performance improvement initiatives and to drive continuous quality improvement in the delivery of the standard of care. The 2013 IOM report reviewed several challenges to the development of cancer care quality metrics, including the failure to address the entire trajectory of cancer care and the underrepresentation of older adults in quality measurement. In particular, the report found that "there are few or no measures for other rare cancers, such as brain and ovarian cancers" (IOM, 2013, p. 281).

The SGO has developed a list of quality indicators for ovarian cancer based on current evidence (see Box 4-3). One study of 123 women with ovarian cancer foud compliance with such quality indicators to be variable (Liang, 2015).

NOVEL THERAPIES

A better understanding of histologic subtypes of ovarian carcinomas and their molecular features (see Chapter 2) has led to a more targeted approach in the development and use of new therapeutic treatments. In light of the growing number of new therapeutics, innovative early-phase clinical trials that incorporate molecular biomarkers of efficacy are needed to help identify which ovarian cancer histologic and molecular subtypes are likely to be resistant or responsive to specific therapies. This section covers research on the newly introduced classes of therapeutics along with novel therapy development strategies and technologies.

Targeted Therapies: Current Approaches

During the past 20 years improvements in the overall survival rates for ovarian cancer have lagged behind those for a number of other solid malignancies (Vaughan et al., 2011). The incremental gain in overall survival for ovarian cancer is largely attributable to changes in chemotherapy schedules and routes of administration (Armstrong et al., 2006). A recent study found that the addition of a third cytotoxic agent (on top of the platinum-taxane standard) provided no benefit in PFS or overall survival (Bookman et al., 2009).

BOX 4-3
SGO Quality Indicators for Ovarian Cancer

1. Operative report with documentation of residual disease within 48 hours of cytoreduction for women with invasive ovarian, fallopian tube, or peritoneal cancer
2. Complete staging for women with invasive Stage I–IIIB ovarian, fallopian tube, or peritoneal cancer who have undergone cytoreduction
3. Intraperitoneal chemotherapy offered within 42 days of optimal cytoreduction to women with invasive Stage III ovarian, fallopian tube, or peritoneal cancer
4. Intraperitoneal chemotherapy administered within 42 days of optimal cytoreduction to women with invasive Stage III ovarian, fallopian tube, or peritoneal cancer
5. Platin or taxane administered within 42 days following cytoreduction to women with invasive Stage I (grade 3), IC–IV ovarian, fallopian tube, or peritoneal cancer
6. Venous thromboembolism prophylaxis administered within 24 hours of cytoreduction to women with invasive ovarian, fallopian tube, or peritoneal cancer
7. Order for prophylactic parenteral antibiotic administration within 1–2 hours before cytoreduction for women with invasive ovarian, fallopian tube, or peritoneal cancer
8. Order for prophylactic parenteral antibiotic discontinuation within 24 hours after cytoreduction for women with invasive ovarian, fallopian tube, or peritoneal cancer

SOURCE: SGO, 2015.

Thus, to maintain progress, researchers have turned to molecularly targeted agents, a number of which have been developed and used to manage various malignancies. Unlike most traditional cytotoxic anticancer drugs, these drugs target tumor cells, tumor stroma, tumor vasculature, and aberrant signaling mechanisms in the tumor. For example, the Cancer Therapy Evaluation Program (CTEP)[1] of the NCI, which sponsors clinical trials for new anticancer agents, focuses on agents that target pathways involved in apoptosis, survival and proliferation, migration and invasion, angiogenesis, mitosis, protein turnover, immunomodulation, DNA repair and epigenetics, and stem cell signaling (see Appendix C for a list of current ovarian cancer clinical trials compiled from www.ClinicalTrials.gov).

[1]For more information, see http://www.ctep.cancer.gov (accessed September 22, 2015).

Anti-Angiogenic Therapy

Angiogenesis (blood vessel development) in tumors increases the perfusion of oxygen and nutrients into tumor cells and thereby promotes tumor growth and facilitates tumor metastasis (Spannuth et al., 2008). Several proteins, such as VEGF and its receptor (VEGFR), play important roles in angiogenesis. VEGF stimulates cellular pathways that lead to the formation and branching of new tumor blood vessels, tumor growth, and increased metastatic potential (Hicklin and Ellis, 2005). It is also hypothesized that anti-angiogenic therapies help to balance angiogenic signaling and normalize the vasculature, thus improving the delivery of anticancer drugs to the tumor (Goel et al., 2012). Anti-angiogenic therapies have also been shown to reverse immunosuppression, which suggests it might be effective to use anti-angiogenic therapies in combination with immunotherapies (Mauge et al., 2014). Accordingly, therapies have been designed to inhibit the VEGF–VEGFR pathway with the goal of producing a rapid and sustained anti-angiogenic and antitumor response, and research has found such an approach to be effective. In particular, anti-angiogenic therapies (e.g., bevacizumab) have been shown to be effective in treating recurrent ovarian cancer both when used as a single agent and in combination with chemotherapy or other targeted agents (Liu et al., 2014a). Although no anti-angiogenic therapies have been approved by the FDA for the frontline treatment of ovarian cancer, the FDA has approved the use of bevacizumab in combination with chemotherapy for the treatment of women with platinum-resistant, recurrent ovarian cancer (Eskander and Tewari, 2014). In Europe, the European Medicines Agency has approved a number of anti-angiogeneic therapies (including bevacizumab) for the treatment of advanced primary, recurrent, and metastatic ovarian cancer (Eskander and Tewari, 2014).

The anti-angiogenic signaling process is complex—it is characterized by multiple pathways that not only overlap but have compensatory mechanisms. Besides the VEGF–VEGFR pathway, a number of other pathways also regulate tumor growth and metastasis and provide compensatory mechanisms when VEGF signaling is blocked. Therefore, recent anti-angiogenic therapies have been designed to simultaneously block both VEGF and VEGFR signaling and other pathways that are critical to angiogenesis and tumor growth. The use of additional anti-angiogenic agents that target VEGFR and other kinases has had variable results (Biagi et al., 2011; Campos et al., 2013; Coleman et al., 2011; Davidson and Secord, 2014; du Bois et al., 2014; Friedlander et al., 2010; Gotlieb et al., 2012; Hirte et al., 2015; Ledermann et al., 2011). This variability in response is most likely a reflection of the highly heterogeneous nature of the disease, the high rate of drug resistance, and the presence of compensatory angiogenic mechanisms. Therefore, dis-

rupting multiple signaling pathways with a combinatorial approach may provide an improved response.

Various challenges remain in finding effective biomarkers or molecular signatures that will predict sensitivity to anti-angiogenic therapies or predict increased risk of toxicity (Aghajanian et al., 2012; Collinson et al., 2013; Eskander and Tewari, 2014; Monk et al., 2014; Pujade-Lauraine et al., 2014). Currently, bevacizumab is licensed as a molecularly unselected agent, meaning that patients are not molecularly stratified into groups to determine if one group responds better than another group. However, certain molecular features may actually predict a tumor's response to treatment (Collinson et al., 2013; Gourley et al., 2014; Symeonides and Gourley, 2015; Wehland et al., 2013). These biomarkers will need further verification, but hopefully, by stratifying patients according to the histologic and molecular subtypes of each ovarian cancer subtype, it will be possible to achieve better outcomes for women with ovarian cancer.

PARP Inhibitors

Another cellular process that is key for the long-term survival of tumors is the cell's DNA repair in response to damage caused by chemotherapeutic agents and genomic instability. The main DNA repair process is high-fidelity (nearly error-free) homologous recombination (HR), which is mediated by several protein products, including those of the *BRCA1* or *BRCA2* genes (Gudmundsdottir and Ashworth, 2006). If the cell does not have a functional HR pathway, alternative damage repair processes are activated, such as base excision repair (BER) and error-prone nonhomologous end joining (NHEJ). The rate-limiting step of BER is the activation and activity of the PARP enzyme (Amé et al., 2004; Dantzer et al., 2000). If both HR and BER are disabled and only NHEJ remains functional, then the already genetically instable tumor cells rapidly acquire enough genetic mutations to cause cell death (Ashworth, 2008; Bryant et al., 2005; Farmer et al., 2005). Thus, researchers expected that drugs of the newly developed class of PARP inhibitors would be effective against tumors with faulty HR repair processes (Ashworth, 2008; Farmer et al., 2005; Feng et al., 2015).

Studies have indeed shown that PARP inhibitors, alone or in combination with chemotherapy, are effective in women with recurrent ovarian cancer, particularly those with a *BRCA1* or *BRCA2* mutation. In particular, olaparib improves PFS when used as a maintenance therapy in the context of *BRCA1* or *BRCA2* mutations, platinum sensitivity, and recurrent disease (Audeh et al., 2010; Fong et al., 2009; Ledermann et al., 2012; Menear et al., 2008). In December 2014, the FDA approved olaparib as a therapy for women with recurrent ovarian cancer who have a *BRCA1* or *BRCA2* mutation and who have had three prior chemotherapy treatments

(FDA, 2014b). Two months before that, the European Medicines Agency had approved olaparib as first-line maintenance therapy for women with platinum-sensitive, recurrent HGSC who are in complete or partial response to platinum-based chemotherapy (EMA, 2014). Additional evidence suggests that the addition of olaparib to chemotherapy improves PFS in platinum-sensitive recurrent ovarian cancer (Oza et al., 2015). Current trials are exploring the use of PARP inhibitors, including in combination with other molecularly targeted agents (see Appendix C). Preliminary evidence suggests that the combination of the anti-angiogenic cedirinab and the PARP inhibitor olaparib may be as effective as cytotoxic chemotherapy regimens (Liu et al., 2014b).

Targeted Therapies on the Horizon

Advancements in technology can catalyze drug discovery. For example, next-generation sequencing (NGS) technologies and data from such initiatives as The Cancer Genome Atlas (TCGA) have allowed researchers to improve their understanding of aberrations and the pathways that are perturbed in ovarian cancer (Cancer Genome Atlas Research Network, 2011). In addition, functional genomics approaches make possible large-scale screening methods based on the loss of gene expression (Cong et al., 2013; Mali et al., 2013; Wood et al., 2011). Immunoscreening has also been used to help identify ovarian-specific immune targets (Sahin et al., 1995). The integration of these approaches with genomic platforms may help researchers identify additional targets.

Precision Medicine

Precision medicine involves the development of molecularly targeted therapies that take into account the variability in genes among individuals. The genomic information derived from modern sequencing technologies aids in the development of precision medicine and may lead to a new paradigm for clinical investigation and for crafting treatment decisions for individual patients. The use of NGS has led to the development of targeted therapies for various solid tumors (Chapman et al., 2011; Garnett et al., 2012; Kwak et al., 2010), and these data may also lead to new indications for already approved cancer drugs if identical mutations exist in other cancer types, including ovarian cancer. The NCI-MATCH trial represents a new method for evaluating targeted therapies, which is needed for precision medicine initiatives. However, it should be noted that some ovarian carcinoma subtypes, such as HGSC, may have limited actionable mutations. While targeting specific genetic changes in defined patient subsets has been successful, there could be a wide range of responses to appropriately

selected therapies. Furthermore, a large number of cancer drugs have not been linked to specific genomic alterations that could be used as biomarkers to specify their potential therapeutic efficacy.

The molecular analysis of HGSC by TCGA Research Network revealed the presence of "*TP53* mutations in almost all tumors (96 percent) [and] low prevalence but statistically recurrent somatic mutations in nine further genes" (Cancer Genome Atlas Research Network, 2011, p. 609). Because p53 is the nexus of various tumor suppressive pathways, it would probably be of benefit to reactivate or restore p53 function in order to revert or rescue cells from resistance to standard chemotherapeutic treatments (Carrillo et al., 2015; Mohell et al., 2015). A clinical trial is currently under way to investigate the use of a p53-reactivating compound APR-246 in ovarian cancer (Aprea, 2014).

As newer mutations are discovered, novel therapeutics may be developed to block the pathways that promote tumor growth and survival. For example, low-grade serous ovarian carcinomas frequently harbor mutations in *KRAS* or *BRAF* and express active mitogen-activated protein kinase (*MAPK*) (Coward et al., 2015). Patients with these carcinomas may benefit from agents that inactivate the ERK1/2 pathway. *PI3K* is found to be mutated in 33 percent of patients with clear cell ovarian cancer, while a loss of *PTEN* gene expression is noted in 40 percent of these patients. Studies of various inhibitors of the PI3K/AKT pathway are ongoing. TCGA data are guiding the development of other molecularly targeted therapies as well. Notable targets include *PI3K*, *BRAF*, *MEK*, *ERK*, and *MAPK*.

Immunotherapy

Cancer immunoediting is a process whereby host immunity functions not only as an extrinsic tumor suppressor but also to shape tumor immunogenicity (Dunn et al., 2004). A central theme of the cancer immunoediting process is that tumor cells express antigens that distinguish them from their nontransformed counterparts, thus permitting their recognition by T cells and their eventual destruction by immunological mechanisms. In ovarian cancer, the presence of intraepithelial CD8+ T cell infiltrates has been shown to correlate with improved survival rates (Hwang et al., 2012; Sato et al., 2005; Shankaran et al., 2001; Zhang et al., 2003). These findings suggest that the endogenous T cell compartment of ovarian cancer patients is able to recognize antigens on the surface of the malignant cells. Therefore, researchers are looking at approaches to generating antitumor immune responses that lead to tumor eradication, including antibody-based therapies, cancer vaccines, immune modulation, and adoptive cellular therapies.

One challenge in evaluating immunotherapeutic approaches to treating ovarian cancer lies in deciding where in the disease course the agent should

be evaluated. A large number of immunotherapeutic strategies are under investigation for women with ovarian cancer (see Appendix C). Most of these trials are pilot studies or small Phase I or Phase II trials with the goal of assessing safety and immunogenicity. Some have correlated improved outcome with a surrogate such as antibody or T cell response, and most current trials aim to produce cellular responses. However, few of these trials are adequately powered, and none has yet shown definitive efficacy.

Another important consideration in the development of immunotherapy is the need for reliable markers of clinical efficacy. Clinical outcomes to immunotherapy are often not accurately assessed by the conventional imaging measures for solid tumors. Indeed, the infiltration of a tumor by active immune cells following therapy may be misleadingly diagnosed as tumor growth and disease progression. These considerations led some researchers to propose a set of immune-related response criteria in an attempt to capture the additional response patterns observed with immune therapy (Wolchok et al., 2009).

Antibody-Based Therapies

The anti-CA-125 antibody oregovomab binds with high affinity to circulating CA-125 and generates both a cellular and a humoral immune response. Its use in ovarian cancer has had mixed results (Baum et al., 1993; Berek et al., 2003, 2004; Ehlen et al., 2005; Mobus et al., 2003; Noujaim et al., 2001). Another anti-CA-125 antibody, abagovomab, failed to demonstrate significant prolongation of PFS or overall survival in ovarian cancer patients in first remission (Sabbatini et al., 2013). Although neither approach showed a survival improvement, interest remains in considering CA-125 as a target for studies with other immunotherapy approaches because CA-125 is overexpressed on most ovarian carcinoma cells and expressed at low levels in other tissue sites, and because preclinical data support its role in the modulation of ovarian tumor growth and invasiveness (Gubbels et al., 2006).

Cancer Vaccines in Ovarian Cancer

The development of ways to analyze humoral and cellular immune reactivity to cancer has led to the molecular characterization of tumor antigens that are recognized by autologous CD8+ T cells or antibodies (Alpen et al., 2002; Boon and van der Bruggen, 1996; Chen et al., 1997; Sahin et al., 1995; Scanlan et al., 2000; Van den Eynde and Boon, 1997; van der Bruggen et al., 1991). When the NCI developed a priority-ranked list of cancer vaccine target antigens (Cheever et al., 2009), the top 10 antigens included WT1, MAGE-A3, and NY-ESO-1, all of which are tumor

antigens that are well known to be expressed in a portion of ovarian cancer patients (Daudi et al., 2014; Hylander et al., 2006; Odunsi et al., 2003). Among these antigens, NY-ESO-1 has been investigated most extensively for patients with ovarian cancer (Odunsi et al., 2007, 2012, 2014; Sabbatini et al., 2012). While studies with these antigens have found that using vaccines to generate integrated humoral and T cell immune responses appears to have some clinical benefit, it is not yet possible to come to definitive conclusions on efficacy because of the small study sizes. In addition, early preclinical and clinical data suggest promise for vaccination with neoantigens, but more study is needed (Castle et al., 2012; Duan et al., 2014; Gubin et al., 2014; Linnemann et al., 2015; Rizvi et al., 2015; Wick et al., 2014). Remaining questions include: Are monovalent or multiantigen vaccine approaches likely to provide better results? At what disease state is vaccination appropriate? What is the optimal frequency and duration of vaccination? How should antigen-specific immune responses be monitored? How should the induced immune response be sustained?

Immune Modulation

Immune modulation acts to reinstate an existing anticancer immune response or to elicit novel responses as a result of antigen spreading. Studies of immune modulation have been carried out in a variety of solid tumors, but there has been more limited research with ovarian cancers. One approach to immune modulation, checkpoint blockade (the inhibition of immunosuppressive receptors expressed by activated T lymphocytes), has been shown to induce robust and durable responses in studies on a variety of solid tumors (Brahmer et al., 2012; Robert et al., 2014). A number of checkpoint-blocking antibodies are approved by international regulatory agencies for use in humans (Hodi et al., 2010; Tumeh et al., 2014). The use of checkpoint-blocking antibodies in treating cancer is expanding, but these agents have not been tested extensively nor have they been approved for use in treating ovarian cancer (Brahmer et al., 2012; Disis et al., 2015; Varga et al., 2015). One challenge in treating ovarian cancer is that because of the heterogeneity of the disease, it is important to identify the full spectrum of immune resistance mechanisms. For example, emerging evidence suggests that the clinical efficacy of immunomodulatory antibodies (especially checkpoint blockers) may be profoundly influenced by the mutational burden and neoantigens specific to the particular cancer subtype (Snyder et al., 2014). A higher neoantigen load can lead to recruitment of a diverse repertoire of neoantigen-specific T cells, and checkpoint blockade may help to restore a favorable ratio of antigen-specific effector cells to regulatory T cells. Researchers do not yet know which patients are most likely to respond to

immune modulation and checkpoint blockade in the treatment of ovarian cancer, so studies on this issue are warranted.

Adoptive Cellular Therapies

Adoptive cell transfer (ACT) involves the live collection, modification, expansion, and activation of circulating or tumor-infiltrating lymphocytes that are then reinfused into patients (Rosenberg et al., 2008). Initial studies demonstrated the potential of T cell immunotherapy to eradicate solid tumors (Dudley et al., 2002, 2005). In order to improve the therapeutic potential of transferred cells, peripheral blood lymphocytes with unique antigen specificity can be genetically modified (Kalos et al., 2011; Robbins et al., 2011; Rosenberg et al., 2008). Although remarkable responses have been observed in patients with other solid tumors (Dudley et al., 2005; Robbins et al., 2011), the FDA has not approved any ACT protocol for use in ovarian cancer patients. An ongoing clinical trial in patients with ovarian cancer may shed some light on the potential role of ACT in this disease (Adaptimmune, 2012). The goals of future studies of ACT in patients with ovarian cancer should include identifying biomarkers of response or nonresponse and determining whether this approach should be combined with other immunotherapy strategies.

Immunostimulatory Cytokines

Immunostimulatory cytokines are generally used as adjuvants for other anticancer immunotherapeutics. Although many attempts have been made to use these cytokines in patients with ovarian cancer, no randomized consolidation study has demonstrated a significant improvement in overall survival (Alberts et al., 2006; Hall et al., 2004).

CLINICAL TRIALS FOR OVARIAN CANCER

Clinical researchers are regularly developing new trial designs in order to accommodate new approaches to the development of anticancer agents, to make the trial designs more efficient, and to study types of therapies that have not been evaluated before. Many of these new approaches are due to the shift away from a primarily empiric development of cytotoxic therapies toward the development of molecularly targeted agents. Limited resources for conducting clinical trials and shrinking patient populations for which precision targeted agents are appropriate have made it more difficult than ever to come up with efficient clinical trial designs. Design complexity and novelty do not guarantee design quality or utility. Thorough evaluation and transparency are needed if one is to choose an optimal clinical trial design

that most efficiently and convincingly answers a specific clinical question. The following sections provide a brief overview of clinical trial design and how study designs are being adapted to increase efficiency and to include biomarker analyses relevant to modern molecularly targeted therapies in ovarian cancer.

Preclinical Studies

Preclinical studies involve the testing of anticancer agents in biological systems such as tumor cell line cultures or animals (see Chapter 2). Although preclinical models do not always accurately represent the human manifestation of ovarian cancer, researchers may still glean much useful evidence regarding anticancer agent activity against tumor cells or on a particular molecular target within those cells. Preclinical studies can also provide greater insights into the mechanisms of action of an agent and into an agent's potential toxicities.

A better understanding of the biological mechanisms underpinning a drug's activity make it easier to develop optimal designs of clinical trials aimed at identifying patients who are most likely to benefit from a new therapy and least likely to experience toxicities. Few patient-derived xenograft models have been developed from HGSCs (Scott et al., 2013). Greater incentives and resources for the creation of such models could benefit ovarian cancer drug development programs and, if the models are successful, could increase the number of promising drugs for human clinical trials.

Clinical Studies

If they meet toxicity and efficacy benchmarks in preclinical studies, novel agents are moved into human clinical studies. These studies are conducted in a series of phases (see Box 4-4) in which new agents are given to various patient populations and examined for the mechanism of action, dose-related toxicities and overall safety, and effectiveness (Rubinstein, 2000).

Phase 0 Studies and Window-of-Opportunity Studies

Phase 0 studies are exploratory first-in-human studies that are intended to bridge evidence from preclinical animal studies; these Phase 0 studies are not conducted with therapeutic intent, and they are intended primarily to examine biological target modulation rather than antitumor activity (Kummar et al., 2007). Phase 0 trials are sometimes embedded as window-of-opportunity (WOO) studies in Phase II or Phase III trials to evaluate the clinical benefit of a new therapy, but WOO trials typically use clinical

BOX 4-4
Clinical Study Phases

Phase 0

- These are exploratory "first time in human" studies to test an agent's mechanisms of action, bioavailability, pharmacodynamics, and pharmacokinetics (no therapeutic intent).
- Small numbers of patients are given subtherapeutic doses for short durations to compare drug metrics with preclinical results.

Phase I

- The primary intent is to assess an agent's toxicity profile, determine the maximum tolerated dose, determine related dose-limiting toxicities, and establish a suitable dose for further human testing.
- Phase I studies usually enroll patients with advanced cancer who have exhausted standard treatment options.

Phase II

- The primary intent is to assess the efficacy of new agents (potentially in combination with each other or standard treatments), gather more data on safety, and determine whether an agent looks sufficiently promising to be further developed in Phase III trials.
- The agent dose is estimated from Phase I studies.
- Phase II studies usually enroll patients who were treated with one or more standard therapies without eradication of their cancer or who have a cancer for which no standard effective therapy exists.

Phase III

- Phase III studies are comparative trials intended to assess the effectiveness of a new agent or agent combination compared to existing standard of care.
- Randomized controlled trials are considered to be the gold standard design for Phase III studies, but in some situations historical control or concurrent control designs may be considered acceptable.

Phase IV

- The main goal is to acquire more real-world experience for a new agent following marketing authorization in order to gain information in a broader patient population that encompasses a variety of disease severities and comorbid conditions, with the goal of better understanding the agent's effectiveness and to identify rare or late-appearing adverse effects.
- Phase IV studies may include studies that collect extended follow-up data on patients who have completed Phase III trials, noninterventional observational studies, large simple trials, and post-marketing surveillance studies.

tumor response or PFS endpoints to establish evidence of antitumor activity for a new agent (Glimelius and Lahn, 2011). In a WOO trial, a patient agrees to delay conventional therapy for a few weeks in order to observe the antitumor effect of a new agent.

Figure 4-1 shows one example of a WOO study embedded in an adjuvant therapy trial. At the investigators' institution, the standard clinical evaluation plan (i.e., the Anderson algorithm) specifies that, prior to any treatment, women who are presumed to have advanced-stage ovarian cancer undergo laparoscopic evaluation to determine the likelihood that the tumor can be completely resected. If the tumor is unlikely to be completely resected (a score of 8 or more), the recommended course of action includes immediate NACT with a novel agent in combination with a standard chemotherapy regimen, followed by debulking surgery. Women who have a low score are offered participation in a WOO study that involves the administration of a novel single agent prior to debulking surgery and the option to enroll post-operatively in a randomized adjuvant therapy study comparing novel therapy to standard therapy. In both cases, tissue samples are collected both at the time of the laparoscopy and at the time of surgery, which allows researchers to examine the in vivo effects of the novel agents and may provide valuable insights into the mechanism of action or resistance for those agents.

Phase I Clinical Trials

Phase I studies attempt to find a dose that provides an acceptable balance between killing tumor cells and patient toxicity by delivering increasing doses of the experimental agent to successive patients while they are

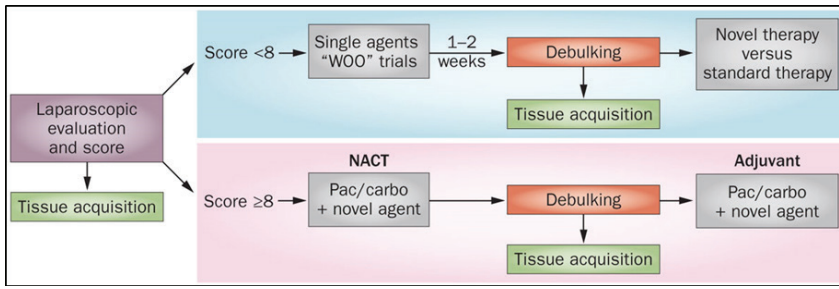

FIGURE 4-1 Novel clinical trial design using the Anderson algorithm.
SOURCE: Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews: Clinical Oncology.* Nick, A. M., R. L. Coleman, P. T. Ramirez, and A. K. Sood. A framework for a personalized surgical approach to ovarian cancer. 12(4):239-245. Copyright 2015.

carefully monitored for signs of toxicity. The dose escalation ceases when the maximally tolerated dose is identified. The various Phase I designs differ in the criteria they use for progressing through a sequence of doses. Three of the most commonly used Phase I study designs are the 3+3 cohort expansion, accelerated titration, and continual reassessment designs (Ivy et al., 2010). The conventional 3+3 cohort expansion design increases doses in successive cohorts of three patients. Accelerated titration designs are characterized by a more rapid initial dose escalation and the potential for doses to be increased within patients in addition to across patients (Simon et al., 1997). The continual reassessment method relies on a continually updated mathematical model that expresses the relationship between dose and the probability of toxicity (O'Quigley et al., 1990). If rapid dose escalation were more widely adopted when there are scant preliminary data to suggest the starting dose level, Phase I studies could be completed more quickly with fewer patients undertreated and with minimal increase in risk of serious toxicities (Horstmann et al., 2005; Kurzrock and Benjamin, 2005; Simon et al., 1997). Phase I clinical trials have increasingly enrolled additional patients in expansion cohorts, but they often lack statistical justification for the cohort size (Dahlberg et al., 2014). The recent PARP inhibitor studies are an example of the successful use of expansion cohorts for ovarian cancer clinical trials (Fong et al., 2010). Clearer guidance is needed so that the expectations for the goals, study designs, and reporting of Phase I trials are better understood and so that the available resources for clinical research are most appropriately utilized.

Phase II Clinical Trials

Randomized Phase II trials allow for a preliminary assessment of the clinical benefits of an experimental therapy relative to other therapies, but they also require larger sample sizes. Single-arm trials with a tumor-response endpoint have been a mainstay of oncology Phase II trials, but newer anticancer agents often do not fit into the traditional paradigm of cytotoxic chemotherapies. Randomized Phase II trials may be needed in situations where it is difficult to specify historical benchmarks for the clinical endpoint of interest or when a new agent will be evaluated in combination with a standard therapy that is known to be effective (Rubinstein et al., 2009). When the new agent is evaluated in combination with a known effective therapy, a single-arm trial cannot determine the relative contribution of the new agent (Rubinstein et al., 2005).

Biomarkers are increasingly being used in Phase II cancer clinical trials, largely because of the rise in the number of molecularly targeted agents under development (McShane and Hunsberger, 2015; McShane et al., 2009). Key considerations in such trials include whether the trial eligibility should

be restricted to only those patients whose tumors possess the presumed target of the new agent and whether trials of targeted agents should be agnostic to type of tumor so that the focus is the target molecular characteristics, regardless of tumor histology. In ovarian cancer clinical trials, biomarkers are occasionally incorporated into the definition of the trial endpoint. Most notably, the biomarker CA-125 has sometimes been used as part of a composite endpoint to indicate the progression of the disease. For example, in the clinical trial GOG-218, the incorporation of CA-125 into the definition of progression resulted in an increased estimate of the treatment's effect (Burger et al., 2011). However, it remains debatable whether incorporating CA-125 in this way strengthens the quality of evidence and whether the composite endpoint more reliably predicts overall survival (Herzog et al., 2014).

Phase III Clinical Trials

Phase III clinical trials are intended to provide definitive evidence about whether an experimental therapy has clinical efficacy when compared to a standard treatment or no treatment. These trials are usually randomized to guard against biases resulting from patient selection. Exceptions to randomization include where there are no known effective therapies or when patients are expected to have extremely good outcomes on standard therapy and a randomized trial would have to be prohibitively large to allow a reliable comparison of the treatments. In the case of ovarian cancer, overall survival and PFS are most commonly used as the primary endpoint for late-phase clinical trials, although the merits of PFS are increasingly being debated (Korn and Crowley, 2013; Korn et al., 2011). (See the discussion of clinical trial endpoint selection later in this chapter.)

An increasing number of Phase III oncology clinical trial designs incorporate biomarkers (producing what is referred to as "biomarker-driven trial designs") under the hypothesis that the biomarkers will help identify a subset of patients who are more likely to benefit from the experimental therapy. However, biomarkers are also used as stratification factors or eligibility criteria to control the variability in expected patient outcomes due to differing baseline prognoses associated with the biomarker values. (See the discussion of prognostic and predictive [treatment-selection] biomarker-based tests later in this chapter.)

The three basic types of biomarker-driven Phase III trial designs are the enrichment design, the stratified design, and the strategy design. The enrichment design randomizes only patients whose tumors are positive for the biomarker, while the stratified design uses a randomization procedure stratified on biomarker values. The strategy design randomizes patients into a biomarker-testing arm or a no-biomarker arm, and patients in the arm

with biomarker testing are assigned to treatment based on a predefined algorithm, depending on the biomarker. The IOM and others have discussed the advantages and disadvantages of the different biomarker-driven designs (Freidlin et al., 2010; IOM, 2012; Sargent et al., 2005). The best choice of design in a particular situation depends on the strength of the evidence supporting the biomarker, the biomarker's relationship to treatment benefit or outcome, and the feasibility of its use (Freidlin and Korn, 2014).

Multiarm Phase II and III Clinical Trial Designs

Extending the conventional single- and two-arm clinical trial designs to three or more arms is relatively straightforward and can offer substantial advantages. In a multiarm trial, a single clinical trial infrastructure can be used, and a greater percentage of patients are assigned to an experimental therapy arm. Multiarm randomized trials are also statistically efficient in that multiple research questions can be addressed with fewer total patients (because data from any treatment arm can be reused) (Freidlin et al., 2008). For example, in GOG-218, women with newly diagnosed Stage III or Stage IV ovarian carcinoma who were unable to have a complete resection of their tumors were randomized to one of three treatment arms (Burger et al., 2011). All three arms included IV paclitaxel plus carboplatin for cycles 1 through 6, plus a study treatment for cycles 2 through 22. The control arm included a placebo for cycles 2 through 22, the second arm added bevacizumab in cycles 2 through 6 and then a placebo in cycles 7 through 22, and the third arm added bevacizumab in cycles 2 through 22. The trial found a prolongation of median PFS by 4 months with use of bevacizumab during and up to 10 months.

A more specialized type of multiarm trial design is a factorial design. In a 2×2 factorial design, four possible combinations of two treatments (e.g., A and B) can be considered: neither treatment A nor B (if appropriate), A alone, B alone, and the combination of A and B. Data from the arm with both therapies can be combined with data from either arm A or arm B to evaluate the effects of the individual therapies as long as the combination of A and B can reasonably be assumed to have an additive effect (Green, 2005). The use of factorial designs is likely to become increasingly important as more effective monotherapies become available and interest turns to the evaluation of combination therapies.

The I-SPY2 Phase II breast cancer trial is the first oncology clinical trial in the United States to use a platform trial structure in which multiple agents can be evaluated seamlessly over time (Barker et al., 2009). This study required the development of protocols that allowed the rapid addition of new investigational agents. In I-SPY2, each arm corresponds to a particular drug under investigation in a randomized comparison against a standard

therapy. Multiple pharmaceutical companies provide their drugs for evaluation, but drugs from competing companies are not directly compared to one another. A platform trial design of this sort is adaptable to any cancer type as long as there are sufficient numbers of promising experimental therapies for inclusion in the trial.

Molecular profiling trials can evaluate large numbers of experimental agents along with the biomarkers intended to guide their use. The biomarkers may be measured using a combination of different assay types. High-throughput assays (e.g., NGS platforms), which are capable of searching tumor DNA and RNA sequences for thousands of potential mutations, are being increasingly used. In molecular profiling trials, patients whose tumors have specific subsets of mutations are assigned to treatment arms that include an experimental therapy designed to target tumors with those specific mutations. There are various types of molecular profiling trial designs, each of which offers different advantages and disadvantages (Kummar et al., 2015).

Phase IV Clinical Trials (Post-Marketing Clinical Studies)

After a drug has demonstrated clinical efficacy and has received regulatory approval to be marketed, additional studies are usually conducted to gain experience with the drug's performance in real-world settings (Suvarna, 2010). These studies may be mandated by regulatory authorities as a condition of drug approval, or the company may choose to acquire more experience with the drug in a broader population under the conditions in which the drugs are likely to be prescribed and used. Post-marketing studies are generally needed because the previous clinical trials typically would involve no more than a few thousand patients, and those patients would have been followed for a limited amount of time. Furthermore, the earlier studies may have excluded sicker patients or patients with a variety of comorbid conditions, providing limited opportunity to observe extremely rare toxicities or toxicities that might appear years after treatment or in the context of certain comorbid conditions. Post-marketing studies are rare, but they may be particularly valuable for use with ovarian cancer treatments due to the cancer's rarity, the relatively small size of ovarian cancer trials, their typically long clinical trajectory, and the substantial potential for late adverse effects associated with many commonly used treatments for ovarian cancer. One post-marketing study that is currently being set up will evaluate the safety and efficacy of bevacizumad in routine clinical practice in patients with advanced ovarian carcinoma, fallopian tube cancer, or primary peritoneal cancer (Hoffmann-La Roche, 2015). The goal of this study is to measure the incidence of adverse events for approximately 18 months after patients begin taking bevacizumab.

Clinical Trial Endpoint Selection

Ovarian cancers frequently recur, and women may experience multiple episodes of disease progression followed by additional therapies. This pattern presents challenges for the selection of interpretable and clinically meaningful endpoints for clinical trials. It may be difficult to assess an experimental agent's effect on overall survival because of the dilution effect of a woman having received multiple therapies. PFS may be a good alternative endpoint in these settings, but in order to be considered clinically meaningful, increases in PFS must be substantial and preferably accompanied by some increase in overall survival or increased quality of life, lower toxicity, or other benefits. Furthermore, if an experimental agent is not expected to shrink tumors, then PFS or overall survival is a more informative endpoint than tumor response. A white paper from the SGO discusses the advantages and disadvantages of a variety of endpoints used in ovarian cancer clinical trials. Table 4-2 summarizes the comparisons made in the white paper; the table does not offer an exhaustive list of all potential endpoints, but rather covers those endpoints that are particularly useful in ovarian cancer studies. For example, disease control rate is increasingly being used in trials with targeted agents. However, its utility has been questioned, and because it may not be beneficial to use in ovarian cancer clinical trials, it was not included in the table (Sznol, 2010). PROs are becoming more appreciated as an endpoint because quality of life is a major factor in the treatments that patients select, but which symptoms are most important to patients and how PROs relate to clinical outcome still need further study. The SGO stressed the importance of considering the meaningfulness of various endpoints and patients' preferences for therapeutics with more dramatic improvements in outcomes relative to existing therapies (Herzog et al., 2014). The importance of limiting toxicities was another clear message, but women surveyed by the SGO indicated that they have a greater tolerance for toxicity related to curative therapy then for toxicity from palliative therapy.

Comparative Effectiveness Studies

In a comparative effectiveness study, the therapies under study have already been shown to have efficacy in the carefully controlled settings of clinical trials, and the goal is to determine which of two or more therapies provides an overall greater benefit (balanced against any risks) in real-world settings (CBO, 2007; Lyman, 2009). These studies can be particularly helpful for diseases like ovarian cancer where there are several available therapies and some significant drug toxicities that need to be weighed against benefits in an objective way. While a randomized trial is considered by many to be the gold standard for a comparative effectiveness study, some

TABLE 4-2
Comparison of Potential Endpoints for Ovarian Cancer Trials

Endpoint	Definition	Advantages	Disadvantages
Response rate	Assessed by the RECIST criteria on the basis of imaging studies, GCIG has defined changes in CA-125 as a response criterion	Objective Quantifiable Results quickly available Tumor shrinkage Appealing to patient and physician	Difficult to measure accurately and reproducibly in ovarian cancer Not considered sufficient as a primary endpoint for Phase III trials Not necessarily a clinically relevant benefit for the patient
Patient-recorded outcomes	Symptom-based parameters	Direct clinical benefit as perceived and quantified by patient	Need randomized blinded studies Subjective and dependent on limited validation instruments
Progression-free survival	Time from entry into trial to progression of disease, death, or lost to follow-up	Provides answer sooner Avoids the impact of post-progression therapy Preferred to time to progression by regulatory agencies	Does not include deaths
Time to progression	Time from entry into trial to progression of disease	Similar to progression-free survival	Does not include deaths
Overall survival	Time from entry into trial to death or lost to follow-up	Clear-cut endpoint of death Indisputably indicative of clinical benefit	Longer time to answer Impacted by post-progression therapy
Time to tumor growth	Uses prescribed longitudinal tumor models	Novel metric In some models is best predictor of OS Reduces time and cost	Not validated in ovarian cancer Subjectivity in assessment

NOTE: GCIG = Gynecologic Cancer Intergroup; OS = overall survival; RECIST = Response Evaluation Critera in Solid Tumors.

SOURCE: Herzog et al., 2014.

argue that large observational studies with access to high-quality data—such as might be obtainable from electronic medical records, registries, and adverse event reporting systems—can also be valuable and may be more reflective of real-world experiences. Such studies require careful modeling of the relationships between outcomes, therapies received, and other clinical

and demographic variables and also extreme vigilance for the possibility of confounding effects that could distort the estimated treatment effects (Korn and Freidlin, 2012; Lyman, 2009).

Adaptive Clinical Trial Designs

Adaptive clinical trial designs are one potential way to make clinical trials more efficient (e.g., fewer patients and shorter duration) or more informative and, ultimately, to deliver effective new therapies to patients more rapidly. There are many types of adaptive designs, but all share the use of outcome measures or other data to make adaptations in the trial quickly (relative to the pace of accrual) (Coffey and Kairalla, 2008; FDA, 2010). Adaptations may include restricting eligibility to a subset of patients who appear to be benefitting most from the experimental therapy, increasing the sample size to more accurately estimate treatment effect, changing the primary endpoint, adjusting or adding drug dose levels, adjusting randomization ratios to favor the treatment arm that appears more promising, or stopping a trial early because sufficient evidence has been obtained to confidently answer the treatment question. Interim monitoring rules, which are applied in nearly all Phase III and many Phase II oncology clinical trials, are one example of an adaptive design feature (Redman, 2012).

Bayesian trial designs are a type of adaptive design that combines information obtained from outside the trial with data accumulating within the trial (Berry, 2006). Traditional designs use only data observed within the trial for decision making, although outside data such as anticipated treatment effects and event rates (e.g., relapses or deaths) may be used informally. Bayesian methods summarize prior beliefs about the values of key parameters such as the treatment effect using formal mathematical models called "prior distributions." As new data are accumulated in the trial, the models are mathematically updated to "posterior distributions" that are used for decision making during the trials and after completion. This mathematical modeling framework offers the flexibility to adapt many aspects of the trial design.

Phase II/III clinical trials, another example of adaptive design, allow for transiting directly from a Phase II to a Phase III trial when an experimental agent demonstrates a positive effect on an intermediate endpoint (Hunsberger et al., 2009; Korn et al., 2012). The intermediate endpoint is the Phase II trial endpoint, most often PFS or tumor response. Key considerations in the design of a Phase II/III trial are the choice of the intermediate endpoint, the target effect size, and the timing of the interim analysis. A biomarker may serve as the intermediate endpoint if there is sufficient evidence that a certain magnitude of effect on the biomarker is likely to translate to a meaningful effect on the definitive Phase III clinical endpoint. A Phase II/

III design is efficient because there is minimal administrative startup time for the Phase III trial and patients accrued during Phase II are combined with the additional Phase III patients for the final analysis.

The flexibility offered by adaptive designs presents some challenges in evaluating their performance. Withouth careful design, adaptive clinical trials are particularly prone to the potential for biased estimates of treatment effects and an increased likelihood of drawing false conclusions (e.g., declaring that a treatment has clinical benefit when it does not) because they are intentionally engineered to repeatedly assess accumulating data in order to alter aspects of the trial. Adaptive designs need thorough and transparent evaluation to ensure that their properties are well understood. These evaluations may require extensive computer simulations conducted under a variety of conditions—both conditions that are consistent with the assumptions made in developing the design and alternative conditions that are still plausible but may differ from the design assumptions (FDA, 2010).

Some adaptive trial design methods are controversial. For example, *outcome adaptive randomization* is the process of dynamically adjusting randomization ratios in favor of treatment arms that appear more promising as data accumulate during the course of a trial. Some have questioned whether these designs are ethical because the randomization may become substantially imbalanced by the end of the trial (Hey and Kimmelman, 2015). While a larger proportion of patients will ultimately be assigned to the better treatment arm (Berry, 2015), a larger total number of patients might be accrued, which would lead to a larger absolute number of patients being assigned to the inferior arm (Berry, 2011; Korn and Freidlin, 2011a,b; Yuan and Yin, 2011). Other risks include biased treatment effect estimates if the characteristics of patients accrued over time drift toward those associated with more favorable prognosis (Rosenberger and Lachin, 1993). The impact of outcome adaptive randomization on analyses of secondary endpoints and associations between patient covariates or biomarkers and outcome is also uncertain. This situation emphasizes the complexities in assessment of adaptive clinical trial designs and the need to evaluate them carefully in order to understand their performance under a range of possible conditions.

Prognostic and Predictive (Treatment-Selection) Biomarker-Based Tests

Prognostic and predictive biomarker tests may aid in making decisions about therapy (IOM, 2010). These tests are also referred to as treatment-selection, treatment-guiding, or treatment-modifier tests and advanced diagnostic laboratory tests. They can be based on a single biomarker or may evaluate a multi-biomarker signature (e.g., omics-based tests, which typically combine multiple biomarker values from omics assays according to

some algorithm or mathematical model) (IOM, 2012; McShane and Polley, 2013). Prognostic tests aim to predict the clinical course of a disease either in the absence of additional therapy (natural course) or in the context of a standard therapy that all patients are likely to receive. Predictive tests indicate a likely benefit or lack of benefit (or potential harm) from a particular therapy relative to other available therapies (Polley et al., 2013). In some situations (e.g., early-phase clinical trials) the term "predictive" is also used to refer to a test designed to indicate whether the patient is likely to respond to a specific therapeutic agent. That response may or may not translate to a clinical benefit such as improved survival. Prognostic and predictive tests must be carefully evaluated to determine whether their use leads to better treatment decisions and to benefits for patients.

There are a few biomarker tests that have been used or are currently under study for their potential to guide treatment decisions for patients with ovarian cancer. Tests for alterations in *BRCA1* and *BRCA2* genes are currently of interest as possible predictive tests that could identify those patients most like to benefit from PARP inhibitors (Michels et al., 2014). The OVA1 test is approved by the FDA for use in guiding referral to a gynecologic oncologist.[2] It is "a qualitative serum test that combines the results of five immunoassays into a single numerical score for women with an ovarian adnexal mass for which surgery is planned as an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy" (FDA, 2011, p. 1). Several chemosensitivity assays have been developed to predict which chemotherapies are likely to elicit a tumor response; however, a review of evidence for the utility of several different chemosensitivity assays concluded that there was insufficient evidence to support a claim that their use would lead to clinical benefits for patients (Kohn, 2014). Few of the studies evaluating these chemosensitivity assays have been randomized clinical trials. An exception is the Tumor Chemosensitivity Assay Ovarian Cancer Study, a randomized biomarker-strategy trial that evaluated whether the use of a chemosensitivity assay that evaluated the impact of 12 chemotherapy agents on cancer cells taken from a patient's biopsy and was then used to direct chemotherapy choices resulted in better outcome for patients with recurrent platinum-resistant ovarian cancer when compared with a physician's selection of chemotherapy (Cree et al., 2007). The trial did not find that the use of the assay resulted in significantly improved PFS or overall survival. Other nonrandomized studies have been conducted in an attempt to assess the value of chemosensitivity tests, but it has gener-

[2]For more information, see http://vermillion.com/providers/ova-1/ova1 (accessed October 7, 2015).

ally been difficult to interpret their results (Grendys et al., 2014; Korn and Freidlin, 2015).

Compared to the strict regulatory requirements for the evaluation of drugs in clinical trials prior to marketing, there is little regulatory oversight in the United States for laboratory tests. In the past several years, a number of unvalidated laboratory tests were prematurely marketed or used in clinical trials, leading to calls for more rigorous development and validation of laboratory tests and for greater regulatory oversight (ASCO, 2015; FDA, 2014a; Hayes et al., 2013; IOM, 2012; Sawyers and van 't Veer, 2014).

Advancing Clinical Trials for Ovarian Cancer

The clinical trial designs described are broadly applicable to a variety of cancer types. How readily they can be applied to ovarian cancer depends on a variety of factors that may evolve over time, including the development of new biological insights and new treatments, particularly molecularly targeted therapies. Certain features of ovarian cancer make some of the designs more readily applicable than others at present. For example, in order to reap the efficiency benefits of platform and molecular profiling trials (e.g., NCI-MATCH), it will be necessary to have a broad selection of novel therapies ready for clinical evaluation, and some promising molecular targets of therapies will need to be identified. Platform trials and molecular profiling trials shift the emphasis away from a tumor's site of origin to its molecular profile, which may be beneficial for relatively rare cancers that may not have a large patient population or resources to warrant its own clinical trial, although advances in the development of novel anticancer agents and therapeutic targets for ovarian cancer have been slow relative to some other cancers, thereby limiting opportunities for the efficient evaluation of new therapies in platform and profiling trials.

There are some features of ovarian cancer that may facilitate novel trial designs, such as the relative accessibility of tumor tissue for molecular analysis for molecularly driven trials and the possibility of carrying out perform WOO trials to directly observe the molecular changes induced by treatment. Such evaluations could help inform the design of trials aimed at preventing or overcoming therapeutic resistance, perhaps by use of multiple therapeutic agents, either in combination or in sequence. A major challenge that is likely to persist is the long clinical trajectory for many women with ovarian cancer. This long trajectory necessitates an extended follow-up in order to observe survival endpoints and makes the interpretation of clinical endpoints particularly complex in those settings where multiple treatments may have been received over a period of several years.

Finally, the improved stratification of women with ovarian cancer may help account for the varying clinical trial outcomes and may ultimately lead

to more clinically meaningful data. For instance, differences in outcomes based on the presence or absence of residual disease after surgery are well documented. Stratification based on whether or not maximum cytoreduction was achieved may be beneficial in accurately assessing clinical trial outcomes. Also, trial designs should account for the various subtypes of ovarian cancer. When looking at individual subtypes, the rarity of cases leads to individual epidemiologic and treatment studies having limited power to draw accurate conclusions. Therefore, the use of consortia and the leveraging of existing data in pooled studies will be important for all studies of ovarian cancer. Such consortia will require infrastructure to support cross-cutting activities such as data harmonization and the development of new statistical methods. New quantitative analysis approaches, including novel statistical, bioinformatic, and computational methods applied to biological, epidemiologic, and clinical data, will be essential for gaining insights into disease etiology, developing biologically driven treatments, and designing efficient clinical trials. Rapidly evolving molecular assay technologies will make it necessary to develop new analysis methods to process and integrate molecular data representing DNA, RNA, and protein profiles of tumors as well as other characterizations, such as tumor epigenetic profiles or host germline genomic profiles. These analyses may provide new insights to help researchers better understand tumor development, growth, metastatsis, and response to therapy. Clinical trials that leverage these new biological insights to optimize treatment selection or adapt to data as they accumulate during the course of the trial may also require novel statistical methods for their design and evaluation.

KEY FINDINGS AND CONCLUSIONS

The committee offers the following findings and conclusions:

- PDS is an effective first-line treatment method, yet maximum cytoreduction may be unachievable in women with Stage III or IV ovarian cancer unless NACT is employed. An evidence-based decision-making strategy or tool to determine which of these options is most appropriate for a patient is needed.
- The majority of women with ovarian cancer respond well to initial treatment with platinum-based (e.g., carboplatin) chemotherapy, although a large fraction of tumors become platinum resistant within 6 months of completing treatment. Given the heterogeneity in both platinum-sensitive and platinum-resistant patient populations at initial diagnosis and recurrence, there is a need for better tools to predict near- and long-term response to treatments for both newly diagnosed and recurrent disease.

- The definition of disease recurrence is generally accepted to be the detection of macroscopic disease within 6 months of complete cytoreduction from initial treatment. There is a debate regarding how the timing of secondary cytoreductive surgery relates to its efficacy in improving patient outcome. As secondary cytoreductive surgery is normally performed at the time of the diagnosis of recurrence, the definition of ovarian recurrence needs to be further refined.
- Given the high rate of drug resistance after the initial response to front-line therapy, additional treatment options are necessary in both the up-front and recurrent settings in order to improve patient outcomes.
- A better understanding is needed of the mechanisms of the development of recurrent disease.
- More well-validated biomarker tests with demonstrated ability to aid in treatment decisions that lead to better outcomes for women with ovarian cancer are needed.
- There is considerable variability in the quality of care provided to women with ovarian cancer nationwide. This variability is influenced by several factors, including the type of hospitals where patients are treated, whether they are treated by a gynecologic oncologist, and whether their care adheres to the proper guidelines. The delivery of more consistent and higher-quality care could have a significant impact on improving outcomes for ovarian cancer patients.
- Significant predictors of nonadherence to the standard of care include advanced age at diagnosis, the presence of one or more treatment-limiting comorbidities, non-white race, and lower socioeconomic status.
- Most ovarian cancers occur in older women, yet little research focuses on how to improve care for older women, especially those with comorbidities, and clinical trials tend to enroll younger patients.
- Given that the effectiveness of novel therapeutics may vary within and among subtypes, it will be necessary to evaluate a variety of approaches, including new combinations of existing drugs, new drug formulations, targeted biologics, protein inhibitors, TP53-directed therapies, anti-angiogenics, immunotherapies, and non-pharmacologic interventions.
- Stratification based on the presence or absence of residual disease after surgery and by tumor subtype may be used to control for the different outcomes in clinical trials and may lead to more clinically meaningful data.
- High-quality preclinical and translational research, improved clinical trial infrastructure, and incentives to facilitate more rapid

accrual of patients to clinical trials are all essential to the rapid delivery of effective new treatments for women with ovarian cancer.

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5

Supportive Care Along the Survivorship Trajectory

Most research on ovarian cancer focuses on improving diagnosis and therapy rather than on managing the side effects of treatment or on the psychological and social (psychosocial) issues that women with ovarian cancer face throughout the trajectory of care and survivorship. Addressing the general problem among all cancers, in 2006 the Institute of Medicine (IOM) concluded that "survivorship research is funded at relatively modest levels within both public and private sectors, especially as contrasted to levels of support for treatment-related research" (IOM, 2006, p. 13). While research on therapies that may provide life-saving benefits to patients is crucial, complementary research to support the quality of their survival—their survivorship—is also a critical concern for women and families affected by ovarian cancer.

This chapter reflects on the research base for the issues of survivorship and management (also known as supportive care) that are particularly relevant across the continuum of care for women diagnosed with ovarian cancer and their families. Because much of the research on survivorship is applicable to individuals with many types of cancer (or other serious diseases), a review of all survivorship literature is beyond the scope of this report. Instead, this chapter highlights the overarching issues in survivorship research and supportive care and discusses the evidence base for specific issues for women diagnosed with ovarian cancer.

DEFINING SURVIVORSHIP

Women are considered ovarian cancer survivors from the time of diagnosis to the end of life. In 2006, the IOM described cancer survivorship as follows:

> Cancer survivorship, as defined in this report, is a distinct phase of the cancer trajectory, but has been relatively neglected in advocacy, education, clinical practice, and research. Raising awareness of the medical and psychosocial needs that may follow cancer treatment will help both survivors and their health care providers to ensure that appropriate assessments are completed and available interventions employed. The constellation of cancer's long-term and late effects varies by cancer type, treatment modality, and individual characteristics, but there are common patterns of symptoms and conditions that must be recognized so that health and well-being can be improved. (IOM, 2006, p. 150)

The IOM study *From Cancer Patient to Cancer Survivor* stated that "although some cancer survivors recover with a renewed sense of life and purpose, what has often not been recognized is the toll taken by both cancer and its treatment—on health, functioning, sense of security, and well-being. Long-lasting effects of treatment may be apparent shortly after its completion or arise years later. Personal relationships change and adaptations to routines and work may be needed. Importantly, the survivor's health care is forever altered" (IOM, 2006, p. 1). That study identified four essential components of survivorship care:

- Prevention of recurrent and new cancers (and other late effects);
- Surveillance for spread, recurrence, or second cancers and assessment of medical and psychosocial late effects;
- Intervention for consequences of cancer treatment (e.g., sexual dysfunction, pain, fatigue, psychological distress, and employment issues); and
- Coordination between specialists and primary care providers to ensure comprehensive care.

For most women with ovarian cancer, survivorship issues do not follow the cancer care continuum (see Figure 1-10 in Chapter 1) in a linear fashion, but rather they are evolving and overlapping from diagnosis to long-term survival (with or without active cancer) or to end-of-life care. The majority of women with ovarian cancer do not fit neatly into the traditional definition of survivorship. They experience survivorship as part of the long-term management of active disease because of the typical pattern of recurrence and multiple cycles of treatment. Consequently, this committee uses the

definition of survivorship proposed by the Society of Gynecologic Oncology (SGO): "the maintenance of physical, social, spiritual, sexual, and economic well-being by addressing short-term and long-term effects of cancer and its treatment" (SGO, 2011, p. 53).

OVERARCHING CHALLENGES IN SURVIVORSHIP RESEARCH FOR OVARIAN CANCER

Much of the research on survivorship that is relevant to women with ovarian cancer is done on individuals with any type of cancer, or else narrowed to women with any type of gynecologic cancer. Most studies that focus on ovarian cancer survivorship do not distinguish between younger and older survivors, who may have markedly different concerns. There also is little information available on the particular supportive care needs that different racial and ethnic groups have, which may contribute to the disparities in care and survivorship that have been observed. Furthermore, studies generally aggregate survivors at different phases of the disease trajectory and usually do not look at survivors by tumor subtype.

In part, these limitations are due to the relatively small numbers of ovarian cancer cases, which limits the power of the research. However, the ovarian cancer subtypes have different outcomes, and studies of women with ovarian cancer in general may not lead to the identification of the unique needs of women living with specific types of ovarian cancer. Finally, most studies on survivorship are retrospective and, therefore, may be biased because only the needs of those who lived long enough to be studied may be reflected in the analyses. Women who had worse prognoses and shorter life expectancies may have had very different concerns that could have been overlooked in a retrospective design.

PALLIATIVE CARE OVERVIEW

An essential part of the comprehensive care of cancer patients is palliative care that begins at diagnosis. The World Health Organization describes palliative care as an approach that "improves the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support from diagnosis to the end of life and bereavement" (WHO, 2002). The IOM identifies palliative care as a component of high-quality cancer care that should span the continuum from diagnosis through end-of-life care (IOM, 2013). The SGO noted that "palliative care significantly improves the quality of life for patients and their families when faced with serious life-threatening illnesses, including advanced gynecologic cancer, and can also substantially reduce the cost of caring for such patients" (Rimel et al., 2015, p. 282). The American

Society of Clinical Oncology (ASCO) recommends that palliative care be included as a routine part of comprehensive cancer care by the year 2020 (Ferris et al., 2009).

Palliative care is not just end-of-life care; the inclusion of palliative care is appropriate at every point in the disease course, including concurrently with cancer therapies, even when the goal of therapy is cure (see Figure 5-1). Women with ovarian cancer can live for years, even with recurrent disease, and can enjoy substantial benefits from supportive care in terms of both symptom relief and life prolongation.

The Value of Integrating Palliative Care

Multiple national and international agencies have recommended that palliative care principles and practice be integrated into the overall care of women with ovarian cancer (Ferris et al., 2009; Levy et al., 2009; Rimel et al., 2015; WHO, 2002). Basic palliative care clinical services delivered by non–palliative care specialists are referred to as *primary palliative care* (PPC), whereas care provided by palliative care specialists is called *specialty palliative care* (SPC). PPC assessments and interventions for women with ovarian cancer need to engage both women and their health care

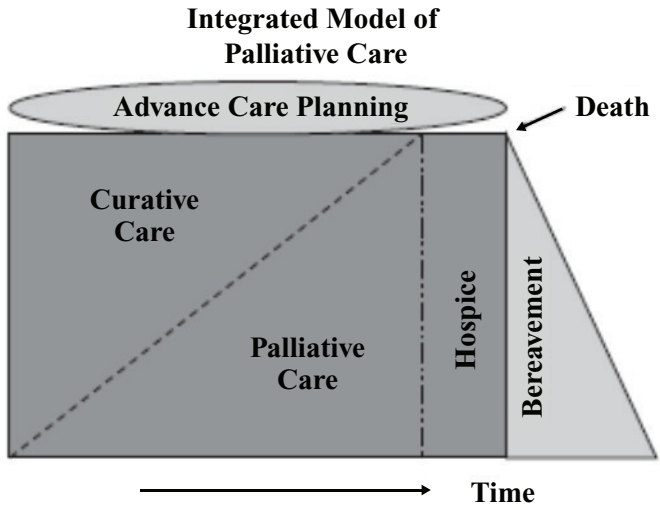

FIGURE 5-1 Integrated model of concurrent palliative and oncology care.
SOURCE: Reprinted with permission. Radwany, S. M., and V. E. Von Gruenigen. 2012. Palliative and end-of-life care for patients with ovarian cancer. *Clinical Obstetrics and Gynecology* 55(1):173-184.

providers. (Later in this chapter, see more on symptom assessment and self-management.)

The general oncology literature indicates that integrating SPC with usual care improves the control of symptoms and a patient's quality of life and understanding of the prognosis and also maintains or improves survival (Bakitas et al., 2009; Brumley et al., 2007; Gade et al., 2008; Meyers et al., 2011; Pantilat et al., 2010; Rabow et al., 2004; Temel et al., 2010; Zimmermann et al., 2014). In addition, palliative care integrated with usual care often costs less overall than usual care alone (Brumley et al., 2007; Morrison et al., 2008, 2011). The few studies that have been conducted on the integration of SPC into the care of women with ovarian cancer show similar findings (Lefkowits et al., 2015; Lowery et al., 2013; Nevadunsky et al., 2014; Rugno et al., 2014). For example, one study of women with platinum-resistant ovarian cancer found that the addition of an early referral to SPC was associated with a cost savings of $1,285 per patient (Lowery et al., 2013).

Barriers to Integration of Palliative Care

Barriers to integrating palliative care into oncology care include limited workforce capacity, policy limitations, and misconceptions among both patients and providers (Hui et al., 2010; Lopez-Acevedo et al., 2013b; Von Roenn et al., 2013). For example, small for-profit and public hospitals are less likely to have inpatient SPC teams, and outpatient SPC is not uniformly available among all types of hospitals and cancer centers (Goldsmith et al., 2008; Hui et al., 2010). Providing SPC consultation remotely via telemedicine may help increase capacity (Hennemann-Krause et al., 2014). Furthermore, current health care policies and reimbursement mechanisms are not structured to support the early integration of palliative care (Lopez-Acevedo et al., 2013b). The limitations include a lack of institutional financial support, poor reimbursement, and a lack of legislation promoting and supporting the integration of palliative care into routine oncology care (Hui et al., 2010; Lopez-Acevedo et al., 2013b; Partridge et al., 2014).

Public knowledge about palliative care is limited, but people react more favorably when terminology other than "palliative care" is used, and they are willing to seek such care if it is recommended by their oncologist (McInturff and Harrington, 2011; Schenker et al., 2014b). Unfortunately, many providers are uninformed about locally available SPC services and mistakenly consider palliative care to be synonymous with end-of-life care and thus incompatible with anticancer therapy (McInturff and Harrington, 2011; Schenker et al., 2014a). Providers also respond more favorably to the use of the term "supportive care" rather than "palliative care" (Dalal et al., 2011; Fadul et al., 2009). The IOM report *Dying in America* con-

cluded that "one of the greatest remaining challenges is the need for better understanding of the role of palliative care among both the public and professionals across the continuum of care so that hospice and palliative care can achieve their full potential for patients and their families" (IOM, 2015).

INFORMATION NEEDS AND SHARED DECISION MAKING

In 2013, an IOM report stated, "A high-quality cancer care delivery system depends upon clinical research that gathers evidence of the benefits and harms of various treatment options so that patients, in consultation with their clinicians, can make treatment decisions that are consistent with their needs, values, and preferences" (IOM, 2013, p. 207). The report also said that "if the goal of clinical research is to improve the quality of cancer care, it is important to produce some of the types of evidence that would be most useful to patients and clinicians when making treatment decisions. For example, patients often want information about the estimated impact of a treatment regimen on their quality of life, functional status, symptoms, and overall experience with the disease, as well as information about other contextual factors" (IOM, 2013, p. 222).

Because ovarian cancer is typically at an advanced stage when it is diagnosed, its treatment requires women to make immediate decisions. As the SGO noted,

> The diagnosis of cancer requires that people become almost instantaneously knowledgeable about their disease, their treatment options, possible toxicities, and likely outcomes. This disease, and the treatment it requires, will have a major impact on their home life, their caretakers, their economic situation and their overall [quality of life], and within this context, decisions need to be made. (SGO, 2011)

Survivorship in ovarian cancer is negatively affected by a lack of available information on the basics of ovarian cancer, especially as compared to other cancers (Ferrell et al., 2003c; Lockwood-Rayermann, 2006; McCorkle et al., 2003; Trivers et al., 2013). Survivors also often lack specific information on such things as fertility preservation options, complementary and alternative treatment options, and the disease's impact on sexual function (Ferrell et al., 2003d; Sun et al., 2007). A longitudinal study of women following a diagnosis of ovarian cancer found consistent information needs including the likelihood of cure, the stage or current status of disease, and information about treatment options (Browall et al., 2004). Medical information is often prioritized over practical physical, social, psychological, or spiritual information, even though younger women and those with lower levels of education may place a higher value on information relating to social and psychological issues (Papadakos et al., 2012). However, physical and psychological symptoms are the most common and severe symptoms

reported by women with ovarian cancer (see sections on specific psychosocial and physical issues later in this chapter). Research shows that providing knowledge about the disease process and teaching coping skills can reduce stress and improve the emotional well-being of women with ovarian cancer (Parker et al., 2006; Roland et al., 2013; von Gruenigen et al., 2010).

Shared Decision Making

In the case of women with ovarian cancer, shared decision making can be complicated because so many of these women present at a late stage of the disease, making it necessary to intervene as quickly as possible. For example, younger survivors report that a rush to treatment often overshadowed their ability to explore fertility preservation options (Sun et al., 2007). While women with ovarian cancer say that they want to come to joint decisions about treatment with their physicians, many still place the highest value on their physicians' recommendations, or even view the decisions as being made solely by their physicians (Elit et al., 2003; Fitch et al., 2003; Jolicoeur et al., 2009; Kitamura, 2010; Luketina et al., 2012; Stewart et al., 2000). In one study of women with ovarian cancer, only 36 percent reported having been very involved in the decision making about surgery, and only 40 percent reported being very involved in decision making about treatment; 20 percent of the women reported no involvement in decision making at all (Andersen et al., 2012). The study further found that women who were involved in decision making about their surgeries, lifestyle, and follow-up care had better emotional health.

In a review of issues for ovarian cancer survivors, Trivers and colleagues commented that "effective survivor–provider communication, including feeling satisfied with the information received and having their disease experiences validated, benefits overall well-being and [quality of life]" (Trivers et al., 2013, p. 2894). However, the quality of the relationship and of the communication between women and their providers can affect how information is exchanged and how care decisions are made. Women who received a positive diagnosis of ovarian cancer long after reporting symptoms to their providers can feel frustrated and angry by the perception of a delayed diagnosis, leading to lower confidence in those providers (Ferrell et al., 2003a). On the other hand, cancer patients undergoing active treatment, including those with ovarian cancer, can be reluctant to complain about their symptoms because of concerns that talking about them might distract their providers away from what they consider to be the more important treatment issues (Gunnarsdottir et al., 2002; Passik et al., 2002; Sun et al., 2007). In a study of women with ovarian cancer on active treatment, women reported experiencing 12 concurrent symptoms on average, but only 61 percent had discussed their most bothersome symptoms with their health care provider in the past month (Donovan et al.,

2005). Equally as concerning, only half of the women who discussed their symptoms with their providers received recommendations for symptom management. Women in this study had low perceptions of control over their symptoms, but those who had received recommendations for symptom management reported significantly higher perceptions of control than those who had not. (See more on symptom assessment and self-management later in this chapter.)

Optimizing the exchange of information and the medical management of treatment and its side effects requires an iterative approach that relies on in-depth conversations between the patient and her interdisciplinary team of providers. Given the current structure of the health care system and the time pressures to move patients through clinics, these types of interactions are difficult to achieve. Furthermore, as discussed in Chapter 4, patient-centered communication and shared decision making in oncology in general are "suboptimal," with clinicians asking for patient preferences in medical decisions only about half the of the time. In part, this is due to "clinicians' lack of training in communication and insensitivity to patients' informational, cultural, and emotional needs" (IOM, 2013, p. 102). As such, it may be useful to involve other health care professionals (e.g., nurses and social workers) to expand on the communication and information provided by physicians or else to use technology (e.g., mobile health technologies) in innovative interdisciplinary models of care so that patient–provider communication between women and their care teams is enhanced.

Efforts to Facilitate Shared Decision Making in Ovarian Cancer

Many efforts are under way to facilitate the dissemination of necessary information so that women with ovarian cancer can better engage in shared decision making. These efforts are aimed both at helping better inform women about their choices and at ensuring that women's individual preferences are included in the decision-making process. In many cases, decision aids are being developed to help women make informed choices. However, while some aids focus on helping women make specific treatment-related decisions (Anderson et al., 2011; Oostendorp et al., 2011), most aids for women with ovarian cancer focus on helping women at high risk for a genetic mutation make decisions about genetic counseling, risk management, and genetic testing (Juan et al., 2008; Tiller et al., 2003, 2006; Wakefield et al., 2008a,b).

Cancer advocacy organizations and policy organizations uniformly encourage self-advocacy, the act of speaking up for your own rights and preferences, as a means of addressing barriers to high-quality, patient-centered cancer care (ASCO, 2015; IOM, 2001; Shapiro et al., 2009). The term originated in the HIV/AIDS, disabilities, and mental health research and advocacy communities and has only recently been adopted into the

cancer lexicon. In these other populations, self-advocacy has been shown to be associated with better symptom management, higher quality of life, and more effective use of health care resources (Brashers et al., 2004; Pickett et al., 2010; Test et al., 2005). One emerging line of research that originated in the ovarian cancer community is aimed at defining the concept of self-advocacy, the skills required for effective self-advocacy, predictors of poor self-advocacy, and the short- and longer-term consequences of self-advocacy in order to help guide the development of interventions (Hagan and Donovan, 2013a,b).

Many different stakeholders act as sources of reliable information and actively work to support women with ovarian cancer in making decisions about their own care. For example, Facing Our Risk of Cancer Empowered, or FORCE, strives to raise awareness and provide resources and information related to genetic counseling and testing for women at high risk for breast and ovarian cancer (FORCE, 2015). The National Ovarian Cancer Coalition's Take Early Action & Live (TEAL) Initiative focuses on creating awareness of the symptoms of undiagnosed ovarian cancer, and its TEAL Totes provide educational materials to women newly diagnosed with ovarian cancer (NOCC, 2015). Other programs focus on increasing awareness among health care providers.

Patient-Centered Outcomes Research Institute

The Patient-Centered Outcomes Research Institute (PCORI), authorized by the Patient Protection and Affordable Care Act,[1] has a mission to help "people make informed healthcare decisions, and improve healthcare delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community" (PCORI, 2015a). Two ovarian cancer–specific projects are funded by PCORI. The American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network, also known as the ABOUT Network, is designed to increase community engagement in research, promote hereditary breast and ovarian cancer (HBOC) research opportunities, and optimize enrollment into HBOC-specific studies as well as to report new research findings to the community (PCORI, 2015b). The other project is developing an ovarian cancer patient-centered decision aid (PCORI, 2015c). The aid will allow patients to assimilate information and identify trade-offs about the impact of combining intraperitoneal and intravenous therapy (versus intravenous therapy alone) on their quality of life and survival, based on their own preferences and personal clinical characteristics.

[1]Patient Protection and Affordable Care Act, Public Law 148, 111th Cong., 2nd sess. (March 23, 2010).

PHYSICAL AND PSYCHOSOCIAL EFFECTS OF OVARIAN CANCER DIAGNOSIS AND TREATMENT

Because women are often diagnosed with ovarian cancer at an advanced stage, the urgency of treating the primary disease or a lack of available expertise may lead to neglect of the management of the physical and psychosocial effects of such a diagnosis and the subsequent treatment. And while many of the effects that women with ovarian cancer experience may be similar to those of individuals undergoing treatment for other types of cancer, women with ovarian cancer may also have specific concerns or needs because of their typically long and recurring periods of active treatment. Unfortunately, as mentioned earlier in this chapter, there is little existing literature on the physical and psychosocial effects of ovarian cancer specifically, and, generally, such literature as does exist seldom takes into account the different ovarian cancer subtypes, different racial and ethnic groups, or different age groups, and it is mostly based on small studies that are insufficient to fully inform practice at this time. The following sections give an overview of the particular physical and psychosocial concerns for women with ovarian cancer. Later in this chapter there is a discussion of interventions aimed at addressing these concerns, and, in recognition of the fact that the accurate assessment of symptoms depends on patient-reported outcomes (PROs), there is also a discussion of the role of PROs and self-management.

Physical Effects of Diagnosis and Treatment

Women with ovarian cancer usually undergo prolonged and intensive courses of active treatment, often for many years (see Chapter 4), and these courses of treatment have numerous side effects that require long-term active management (Chase and Wenzel, 2011). Most commonly, these side effects are similar to those experienced by other cancer patients undergoing chemotherapy and include pain, fatigue, peripheral neuropathy, abdominal symptoms, nausea, hair loss, weight loss, and loss of appetite (Arriba et al., 2010; Badr et al., 2006; Ferrell et al., 2003a; Lockwood-Rayermann, 2006; Otis-Green et al., 2008; Sun et al., 2007). Younger survivors may experience different side effects than older survivors, and the effects may also vary by ovarian cancer subtype (Matei et al., 2009).

Neuropathy is a particularly concerning side effect for women undergoing treatment for ovarian cancer and is especially prevalent because of the typical course of multiple cycles of chemotherapy over many years (Ezendam et al., 2014; Josephs-Cowan, 2006; Nurgalieva et al., 2010; Pignata et al., 2006; Postma et al., 1999; Verstappen et al., 2003; Visovsky and Daly, 2004; Wenzel et al., 2007). Fatigue is also of high concern for

women with ovarian cancer (Anderson and Hacker, 2008; Clevenger et al., 2012, 2013; Liavaag et al., 2007; Payne, 2002; Schrepf et al., 2013; Shinde et al., 2015; Sun et al., 2005). Pain is another particular concern, especially toward the end of life (Portenoy et al., 1994; Rolnick et al., 2007). Some of these side effects can last for years, even after treatment has ceased (Shinde et al., 2015).

The morbidity and mortality of ovarian cancer depends in part on a woman's physical health. For example, in a study of 30-day morbidity in onco-geriatric surgical patients (including women with ovarian cancer), baseline physical function prior to surgery was an accurate predictor of major complications (Huisman et al., 2014). Among women with Stage III ovarian cancer, baseline physical well-being has been associated with overall survival (von Gruenigen et al., 2012). Overall survival was lower for women in the lowest quartile of baseline physical well-being compared with those in the highest quartile. Cancer prehabilitation (i.e., the assessment of baseline functional level in order to identify impairments and provide targeted interventions to improve health and prevent future impairments) has shown promise in patients with gastric cancer (Silver and Baima, 2013; West et al., 2015) and might be applicable to women with ovarian cancer.

Psychosocial Effects of Diagnosis and Treatment

The diagnosis and treatment of cancer in general leads to a wide range of psychosocial effects with a significant impairment in quality of life. The 2008 IOM report *Cancer Care for the Whole Patient* reported:

> [I]ndividuals diagnosed with cancer often report that their care providers do not understand their psychosocial needs; do not consider psychosocial support an integral part of their care; are unaware of psychosocial health care resources; and fail to recognize, adequately treat, or offer referral for depression or other sequelae of stress due to illness in patients and their families. (IOM, 2008, p. 5)

Quality of Life and Personal Growth

In a review of the social and psychological needs of ovarian cancer survivors, Roland and colleagues noted that "despite the many challenges of living with [ovarian cancer], survivors often experience personal growth through their spiritual lives, personal relationships, and renewed perspectives on life" (Roland et al., 2013). Ovarian cancer survivors report a good quality of life overall, and an improved quality of life is most likely to be reported when a patient has supportive relationships, a reprieve from treatment, and a lack of physical side effects (Bodurka-Bevers et al., 2000; Champion et al., 2007; Ferrell et al., 2005; Fox and Lyon, 2007; Kornblith

et al., 2010; Otis-Green et al., 2008; Roland et al., 2013; Stewart et al., 2001; Von Gruenigen et al., 2009, 2010; Wenzel et al., 2002). The stage at which ovarian cancer is diagnosed also shows mixed associations with quality of life, and younger survivors report lower quality of life than older survivors (Bodurka-Bevers et al., 2000; Ferrell et al., 2005; Mirabeau-Beale et al., 2009; Roland et al., 2013; von Gruenigen et al., 2010).

Women often cope in survivorship by being active, spending time with family, supporting other survivors, participating in advocacy, and "living for the moment" (Ferrell et al., 2003b; Roland et al., 2013). Findings on spirituality and ovarian cancer survivorship are mixed; some women who have experienced ovarian cancer report feeling increased meaning and purpose of life, with faith providing strength and hope, while others report a loss in spiritual faith (Champion et al., 2007; Ferrell et al., 2003d; Kornblith et al., 2010; Matulonis et al., 2008; Monahan et al., 2008; Seibaek et al., 2012; Swenson et al., 2003; Wenzel et al., 2002).

Social Supports and Relationships

Social supports and relationships have a positive impact on self-esteem, depression, anxiety, and the overall health of cancer survivors (Champion et al., 2007; Nausheen et al., 2009; Norton et al., 2004, 2005; Pinquart and Duberstein, 2010a; Roland et al., 2013). Given the relative rarity of ovarian cancer, many women with the disease report feeling isolated and seek out other survivors, but many lack access to support groups or other resources (Ferrell et al., 2003b,c,d; Jackson et al., 2007; Roland et al., 2013; Swenson et al., 2003; Wenzel et al., 2002). Advocacy organizations have been particularly important in providing a community for women with ovarian cancer to come together, both at the national level and at the local level (see Chapter 1). For example, the Ovarian Cancer National Alliance provides an online community for women with ovarian cancer in general, including a specific group for women diagnosed with granulosa cell tumor (OCNA, 2015). Given the rarity of ovarian cancer, such online resources can provide a community for women who might not otherwise have access to speaking with other women with similar diagnoses. Social supports from family and friends are also important, such as the caregiving often provided to women with ovarian cancer. (See Chapter 4 for more on family caregiving.)

These sorts of supports can also influence the course of the disease itself. Women with ovarian cancer who report low levels of social support have been shown to have alterations in markers of inflammation, angiogenesis, invasion, innate immunity, and gene expression (Costanzo et al., 2005; Lutgendorf et al., 2002, 2005, 2008, 2009, 2011). One of the first studies to link social supports to ovarian cancer disease outcomes, a prospective study of 168 women newly diagnosed with ovarian carcinoma,

found a lower likelihood of death among those women with higher social attachment, defined as "an individual's experience of emotional connection to others that provides a sense of well-being, intimacy, or security" (Lutgendorf et al., 2012). By contrast, instrumental support, defined as "availability of help, information, and advice from other people," was not associated with survival. It is worth noting that controlling for depression did not change the relationship between social attachment and survival, that the distribution of marital relationships was similar among women with high and low levels of social attachment, and that even moderate reductions in social attachment placed women in the high-risk category. These findings have important implications for screening women for deficits in social attachment and identifying interventions to strengthen or supplement women's existing support networks.

Psychological Distress

Ovarian cancer survivors have high levels of depression and anxiety as compared with the general population and non-gynecologic-cancer survivors (Bodurka-Bevers et al., 2000; Ferrell et al., 2005; Norton et al., 2004; Roland et al., 2013), and younger survivors tend to have higher levels of distress and depression than older survivors (Bodurka-Bevers et al., 2000; Norton et al., 2004; Ponto et al., 2010). The point of diagnosis can be particularly stressful because of the sudden change in health status and feelings of losing control (Ferrell et al., 2003b,d, 2005; Norton et al., 2004; Wenzel et al., 2002). Associations between psychological distress and the stage of disease at diagnosis have been variable (Bodurka-Bevers et al., 2000; Kornblith et al., 2010; Norton et al., 2004). Roland and colleagues noted that "[ovarian cancer] survivors experiencing greater physical symptoms have higher levels of distress, depression, and anxiety, possibly because of symptoms being perceived as disease progression" (Roland et al., 2013).

Ovarian cancer survivors, especially younger survivors, commonly report distress related to fears about recurrence and death (Kornblith et al., 2010; Matulonis et al., 2008; Otis-Green et al., 2008; Shinn et al., 2009; Wenzel et al., 2002). These fears may persist for years after diagnosis and affect quality of life even when the woman is living without evidence of disease (Ferrell et al., 2003b,d; Wenzel et al., 2002). Women may also be distressed by waiting for test results, such as with surveillance for recurrent disease by monitoring CA-125 levels (see Chapter 3) (Parker et al., 2006).

Survivors may experience guilt or fear related to their genetic predisposition for ovarian cancer. In families with a history of ovarian cancer, survivors report feeling sympathy for family members as they recalled their own pain in supporting other relatives with ovarian cancer, and they also feel guilty about passing genetic mutations to their daughters (Ferrell et al.,

2003b,c,d; Sun et al., 2007; Trivers et al., 2013). Women with germline mutations expressed further fear and concern for the lack of effective screening for their family members (Ferrell et al., 2003d). (See Chapter 3 for more on genetic counseling and testing for family members.)

Reproductive and Sexual Health

Studies of the reproductive and sexual concerns of women with cancer often include women with all types of gynecologic cancer or, even more broadly, women with any type of cancer. Thus, women with ovarian cancer may be underrepresented in these studies (Abbott-Anderson and Kwekkeboom, 2012; Deshpande et al., 2015). Survivors of ovarian cancer at all ages have many concerns about their sexual health, including treatment-induced menopause, pain or discomfort during sex, poor body image, decrease in sexual desire and satisfaction, and difficulty in communication about sexuality with a partner (Buković et al., 2008; Carmack Taylor et al., 2004; Ferrell et al., 2003c; Gershenson et al., 2007; Kornblith et al., 2010; Liavaag et al., 2008; Matulonis et al., 2008; Mirabeau-Beale et al., 2009; Roland et al., 2013; von Gruenigen et al., 2009; Wenzel et al., 2002; Wilmoth et al., 2011). Younger survivors report particular concerns about decreases in sexual desire, activity, and pleasure (Champion et al., 2007; Gershenson et al., 2007; Monahan et al., 2008; Swenson et al., 2003).

Infertility or reproductive concerns are pronounced among younger ovarian cancer survivors (Trivers et al., 2013). Young survivors who desire children report that infertility is more distressing than the initial diagnosis itself, and many experience anger or regret about not receiving information or exploring options for fertility preservation prior to treatment (Sun et al., 2007). Fertility preservation may be feasible through conservative surgery or the cryopreservation of oocytes, embryos, or ovarian tissue (Alvarez et al., 2014; Dittrich et al., 2015; Henes et al., 2014; Lambertini et al., 2015; Letourneau et al., 2015; Morice et al., 2011; Prasath et al., 2014). ASCO guidelines state that all cancer patients of childbearing age should receive information about fertility preservation options, yet in practice this does not always happen (Lee et al., 2006; Quinn et al., 2008; Schover et al., 1999; Tomao et al., 2015). Unfortunately, little is known about the extent to which young women with ovarian cancer receive fertility preservation counseling or the impact of counseling on important psychological outcomes during survivorship. One review found that women with ovarian cancer who received fertility preservation counseling had a reduction in long-term regret, regardless of age or parity (Deshpande et al., 2015). As most women with ovarian carcinomas are diagnosed at later ages (see Chapter 1), issues of fertility preservation may be most relevant for women with less common types of ovarian cancer, most notably germ cell tumors,

which tend to occur in teenage girls or young women. One review of 145 women with malignant ovarian germ cell tumors found no difference in menstruation, pregnancy, or offspring after fertility-preserving treatment (Zhang et al., 2012).

Finances and Employment

Ovarian cancer treatment often affects women's ability to work (Trivers et al., 2013). Some survivors report needing to take time off from work to receive care, and other survivors retire after diagnosis (Ferrell et al., 2003c; Matulonis et al., 2008; von Gruenigen et al., 2009). However, research shows that survivors often remain in the workforce or report a need to return to work for economic reasons (e.g., to recover lost wages and maintain insurance coverage), but also as a means of returning to a "normal" life (Ferrell et al., 2003c). Employment and higher income are associated with a higher quality of life for women with ovarian cancer (Ferrell et al., 2005; von Gruenigen et al., 2009). Younger survivors particularly report needing to change jobs because their ability to work was affected but also report fearing that a change of employment might result in the loss of health insurance coverage (Matei et al., 2009).

INTERVENTIONS FOR SUPPORTIVE CARE AND IMPROVING OUTCOMES

Researchers need to better understand how to manage the side effects of disease and treatment, as well as how to develop interventions that can improve disease and treatment outcomes for women with ovarian cancer. Many of the physical and psychosocial effects of ovarian cancer diagnosis and treatment may be better managed by combining pharmacologic and non-pharmacologic therapies, but studies provide little insight into best practices. The following sections describe strategies for managing the physical and psychosocial side effects of treatment, including specific activities that might alleviate symptoms, and how modifying behaviors may affect outcomes.

Pharmaceutical Interventions

The management of the physical side effects of treatment for ovarian cancer often follows the same course as for patients with any other type of gynecologic cancer or even any type of cancer in general, because the most common side effects arise from treatments that are common to all the different types of cancer (e.g., chemotherapy). Studies have looked specifically at the question of how to help women with ovarian cancer deal with the nausea and vomiting that often accompany treatment (Choi et al.,

2014; Timmins et al., 2008; Walker and Lane, 2007; You et al., 2009), pain (Rolnick et al., 2007), and malnutrition (Gadducci et al., 2001). While much can be learned from the literature that is not specific to ovarian cancer, more research is needed on how to improve the pharmaceutical management of some of the side effects of current therapies. Furthermore, there should be more effort placed on developing new disease therapies and approaches that have lower levels of side effects rather than on developing new therapies to manage the side effects of current therapy options (Chase and Wenzel, 2011; Chase et al., 2012, 2015; Teefey et al., 2013). (See Chapter 4 for more on clinical trials and the development of newer therapies with lower levels of toxicity.)

Non-Pharmaceutical Interventions

In addition to taking advantage of decision-making aids (see earlier in this chapter), ovarian cancer survivors can also participate in various activities that not only can help manage the effects of their diagnosis and treatment, but also may improve outcomes. Such efforts are generally not well developed, but there are a number of areas, described below, that warrant further study. (See Chapter 3 for more on the potential role that some of these areas can play in modifying the risk for developing ovarian cancer.)

Complementary and Alternative Medicine

Like other cancer patients, women with ovarian cancer often explore a number of nonstandard treatments (e.g., acupuncture, yoga, vitamins, herbs) to manage their symptoms or even in an attempt to cure the disease (Arriba et al., 2010; Chan et al., 2011; Ferrell et al., 2005; Helpman et al., 2011; Helpman Bek et al., 2009; Lu et al., 2009; Matulonis et al., 2008; von Gruenigen et al., 2006; You et al., 2009). These approaches need to be studied for their potential benefits in managing the side effects of treatment or even improving outcomes, but they may also need to be evaluated for any potential negative interactions with prescribed medications (Andersen et al., 2013).

Exercise

Exercise and yoga have been associated with improvements in physical functioning and qualify of life as well as decreases in pain, fatigue, anxiety, and depression among women with ovarian cancer (Danhauer et al., 2008; Lowe et al., 2012; Sohl et al., 2010, 2012; Stevinson et al., 2009). On the other hand, a review of the literature finds mixed evidence for associations—either a positive association or no association, depending on the

study design—between recreational physical activity and ovarian cancer risk and survival, but the authors emphasized "the greater body of scientific evidence which has demonstrated that [recreational physical activity] results in a plethora of health benefits that can be achieved in all populations, including those with cancer" (Cannioto and Moysich, 2015). (See below for more on sedentary lifestyle.)

Nutrition

Few studies have looked at the role of nutritional assessment in ovarian cancer as part of the treatment plan or at the impact of treatment on nutritional status (Billson et al., 2013; Geisler et al., 2007; Glaser et al., 2012). However, poor nutrition, sedentary lifestyle, and obesity have been associated with a poorer quality of life and survival among women with ovarian cancer (Nagle et al., 2015; Pavelka et al., 2006; Smits et al., 2015; Torres et al., 2013). (See Chapter 4 for more on obesity as a factor in caring for women with ovarian cancer.)

Sleep

Treatment-related sleep disturbances can lead to fatigue, depression, and decreased quality of life for women with ovarian cancer (Clevenger et al., 2013; Mizrahi et al., 2013; Sandadi et al., 2011). Interventions to improve sleeping patterns may help improve quality of life and even treatment outcomes.

Biobehavioral Pathways and Outcomes

Psychosocial and biobehavioral factors can influence the tumor microenvironment and tumor progression (Lutgendorf and Andersen, 2015). In particular, given the evidence of their association with cancer progression and cancer death, three important psychosocial and biobehavioral factors—stress, depressive symptoms, and social support or attachment—are promising targets for intervention (Chida et al., 2008; Pinquart and Duberstein, 2010a,b). These factors are known to modulate tumor characteristics such as angiogenesis, metastasis, and immune response. For example, ovarian tumors in chronically stressed animals have been shown to be larger, more highly vascularized, and having an enhanced expression of proteins known to promote aggressive tumor behavior (Thaker et al., 2006). Similarly, ovarian cancer patients reporting depression and low social support had higher levels of proteins associated with angiogenesis, tumor growth, and immune response (Costanzo et al., 2005; Lutgendorf et al., 2002, 2008). Epidemiologic studies show that improved social support is associated with longer

survival in many cancers, including ovarian cancer (Lutgendorf et al., 2012; Pinquart and Duberstein, 2010a).

Psychosocial interventions have been shown to improve the survival of breast cancer patients, but the results of the studies are inconsistent (Andersen et al., 2008). Unfortunately, to date, few intervention studies in ovarian cancer have been adequately designed to test the same mechanisms. More research is needed on the relationship between biobehavioral factors and signaling pathways in ovarian cancer if researchers are to identify therapies that can block the interactions that promote tumor growth. In addition, research to identify how best to monitor and assess patterns of behavior (e.g., using smart phones and sensors) may provide insight into the relationship between biobehavioral and lifestyle factors. Work investigating how exercise and diet may influence not only patient survival but also tumor response to therapies is needed in order to identify potential novel nonpharmacologic approaches to complement pharmacologic approaches. One current example of such research is a Phase III clinical trial that is studying the impact of changes in diet and physical activity on progression-free survival for patients with previously treated ovarian, fallopian tube, or primary peritoneal cancer (GOG, 2015).

SYMPTOM ASSESSMENT AND SELF-MANAGEMENT

The systematic assessment of symptoms and quality of life in ovarian cancer patients has so far not been a major focus in clinical practice or research. Providers need to ask women about their symptoms, and survivors need to report any new information about their symptoms to their providers in order to inform the process of developing a treatment plan or supportive care interventions. Furthermore, women need to make their personal preferences for care known to their providers. For example, some women may be willing to forego aggressive treatment in order to enjoy, in their opinion, a better quality of life. The following sections discuss the role of the patient in the assessment and management of symptoms (including some of the strategies discussed in the previous sections of this chapter) and in discussing personal preferences for care plans.

Patient-Reported Outcomes

The U.S. Food and Drug Administration defines PROs as the "measurement of any aspect of a patient's health status that comes directly from the patient without the interpretation of the patient responses by a physician or anyone else" (FDA, 2009). Paying attention to PROs will be an important way to inform the development of newer therapies with side-effect profiles that are more acceptable to patients. In 2010 the IOM noted that for cancer

clinical trials in general, "publicly funded clinical trials play a vital role by addressing questions that are important to patients but are less likely to be top priorities of industry," including trials focusing on quality of life (IOM, 2010, p. 10). In 2013, the IOM called on the National Cancer Institute (NCI), PCORI, and others to "develop a common set of data elements that captures [PROs], relevant patient characteristics, and health behaviors that researchers should collect from randomized clinical trials and observational studies" (IOM, 2013, p. 12). Collecting PROs is also important for the management of the symptoms of disease and treatment that providers may be unaware of.

PROs facilitate the systematic assessment of symptoms and impairments in quality of life in clinical and research settings (Cleeland and Sloan, 2010; FDA, 2009; Friedlander and King, 2013; King et al., 2014; Williams et al., 2013). Providers tend to rely on asking open-ended questions, which can lead to significant underreporting of symptoms (Homsi et al., 2006). In the research setting, the use of adverse event reporting using the Common Terminology Criteria for Adverse Events (CTCAE) is commonly used as a substitute for the assessment of patients' symptoms and quality-of-life experiences. However, the use of CTCAE can be unreliable, clinicians may underestimate CTCAE symptoms compared with what is indicated in patient self-reporting, and patients can be better than physicians at detecting serious impairments (Atkinson et al., 2012; Basch, 2010).

The systematic assessment of PROs is essential to ensure safety, to identify and intervene on life-affecting symptoms, to inform shared decision making, to accurately identify and report treatment-related toxicities, and to inform the design and conclusions of clinical trials (see Chapter 4). The NCI sponsored the development and validation of a patient-reported version of CTCAE for use in clinical trials (Dueck et al., 2015), and the Patient-Reported Outcomes Measurement Information System is a national initiative to develop tools for assessing key PROs (Cella et al., 2010; Wagner et al., 2015). Unfortunately, little is known about how best to support clinicians and patients in integrating systematic assessment of PROs into clinical settings or about the optimal timing and frequency of assessments.

PROs in Ovarian Cancer

The NCI's Symptom Management and Health-Related Quality of Life Steering Committee convened a group of experts to identify a core set of symptoms to be assessed routinely in cancer clinical trials for three cancers with a high symptom burden: ovarian, head and neck, and prostate (Reeve et al., 2014). The review of symptoms in ovarian cancer largely focused on women with recurrent disease (Donovan et al., 2014b). The panel recommended prioritizing three areas of symptoms to be monitored with

PROs: symptoms similar to those experienced in other cancers, abdominal symptoms, and symptoms particularly prevalent or important to women with ovarian cancer. Again, many of the most important symptoms for women with ovarian cancer were the same as those for patients with all types of cancer (Reeve et al., 2014). The committee's list of PROs that are particularly important to assess for women with ovarian cancer included abdominal pain, bloating, cramping, fear of recurrence/disease progression, indigestion, sexual dysfunction, vomiting, weight gain, and weight loss (Donovan et al., 2014b).

The inclusion of PROs like these into clinical trials is not new, but the importance of including them has become more widely appreciated and accepted (Friedlander and King, 2013). However, assessment is not enough. Assessment without adequate strategies for managing unmet symptom and quality-of-life needs will lead to frustration for patients and clinicians alike, which only underscores the need to identify better approaches to symptom management for women with ovarian cancer. Furthermore, as more novel agents are used to treat ovarian cancer, new and distinct side effects may arise. The assessment of PROs specific to ovarian cancer will complement the typical primary outcome of concern—survival—and will provide useful data on the benefits and risks of new treatments (FDA, 2009). Therefore, PROs need to evolve along with the nature of symptoms (Donovan et al., 2014b; Han et al., 2009).

Individual Preferences

Ovarian cancer affects women of all ages, races, and social statuses. As such, preferences regarding treatment types and the importance of quality of life versus quantity of life can vary from woman to woman. For example, younger women with ovarian cancer tend to focus on fertility, the impact to family life, and employment (Trivers et al., 2013). One study found that religious beliefs can affect treatment decisions, particularly care near death (Phelps et al., 2009). Because many ovarian cancers tend to recur, women's preferences can change over the course of treatment, depending on the stage of the cancer and the number of recurrences. Still, survivors tend not to transition to palliative care even in the face of an unfavorable prognosis (Sun et al., 2007). Therefore, regular discussion needs to occur between the woman and her care team to ensure that her needs are being addressed, and treatment options need to be tailored to the prognosis, needs, and desires of each woman.

Self-Management

Self-management is broadly defined as an individual's engagement in the management of the symptoms and consequences of a health problem, including treatment and the wide range of psychological, social, physical, and lifestyle and role changes (Barlow et al., 2002). Necessary skills for self-management include forming effective partnerships with health care providers, adhering to medication and treatment recommendations, problem solving and decision making, and taking action (Lorig and Holman, 2003). A key aspect of self-management is that it works best in conjunction with family members and providers encouraging the individual patients to become informed about their conditions, engage in a lifelong process of self-monitoring and self-evaluation, and shift from a perspective of illness to one of wellness (Davis et al., 2000; Dunbar et al., 2008; Grey et al., 2006; Lorig and Holman, 2003; Wiecha and Pollard, 2004). (See Chapter 4 for more on the role of family caregivers in providing needed supports.) In 2003, the IOM report *Priority Areas for National Action: Transforming Health Care Quality* called for providing greater support for self-management (IOM, 2003).

A great deal of research supports the value of providing self-management training for various chronic diseases, such as diabetes and depression (Barlow et al., 2002; Bodenheimer et al., 2002; Davis et al., 2000; Ferguson, 2011; Fredericks et al., 2012; Houle et al., 2013; Lorig and Holman, 2003; Norris et al., 2001, 2002; Schulman-Green et al., 2012; Steed et al., 2003; Wiecha and Pollard, 2004). As cancer survival rates have increased over the past 20 years, researchers, clinicians, and survivors have come to see the value of adopting the chronic care model of self-management into supportive care services for patients with cancer, and self-management interventions to improve coping with cancer-related symptoms have shown promising results (Cimprich et al., 2005; Cockle-Hearne and Faithfull, 2010; Foster and Fenlon, 2011; Hoffman et al., 2013; Koller et al., 2012; Lee et al., 2013; van den Berg et al., 2012).

A recent review of 32 self-management intervention studies characterized self-management interventions in three areas: skills needed during treatment, skills needed during the transition from primary treatment to survivorship, and skills for persons with advanced cancer approaching the end of life (McCorkle et al., 2011). Only one of these studies focused on women with gynecologic cancers (McCorkle et al., 2009). In this particular study, advanced practice nurses provided home visits and telephone calls for 6 months following surgery for gynecological cancers in order to teach self-management skills for dealing with the short- and long-term physical and

psychosocial symptoms associated with treatment. Uncertainty[2] decreased in the intervention group, and for those with high baseline distress, the intervention resulted in improvements in symptom distress and in mental and physical distress over time. More recently, a pilot study of the Written Representational Intervention To Ease Symptoms (WRITE Symptoms) program showed that providing Web-based symptom management support for women with ovarian cancer resulted in lower symptom-related distress (Donovan et al., 2014a). In this study, women with recurrent ovarian cancer were connected to nurses via private Internet message boards for 8 weeks to learn how to monitor and manage their symptoms. The Gynecologic Oncology Group recently compared a nurse-delivered WRITE Symptoms intervention with a self-directed, computer-mediated WRITE Symptoms intervention to see how effective each was in decreasing symptom severity, distress, consequences, and depression and improving quality of life among women with recurrent ovarian, fallopian tube, or primary peritoneal cancer (NIH, 2013). Primary findings from this study are pending.

While small improvements are possible with self-management skills training alone, making substantial improvements requires ongoing interactions between patients and clinicians as well as care delivery modifications designed to support patients and families in their self-management efforts (McCorkle et al., 2011). Future research could identify ways to disseminate and implement promising theory-guided interventions in clinical practice. One challenge to this approach is that the amount of work required for self-management during a time when the disease and the treatment are physically, cognitively, and psychologically overwhelming can be burdensome (Granger et al., 2009; Maeng et al., 2012; Russell et al., 2005). Thus, there is a pressing need for research on interventions that focuses not only on enabling self-management but also on elucidating the mechanisms by which interventions can support self-management behaviors (Hammer et al., 2015). Finally, many interventions that promote the self-management of chronic diseases are effective in the short term, but the self-management behaviors typically diminish over time (Ory et al., 2010; Tang et al., 2012), and the strategies and theoretical mechanisms for sustaining self-management behaviors are not well understood. In 2014, the National Institutes of Nursing Research convened a workshop to discuss the state of the science in self-management; the participants identified a number of areas of research needed to advance self-management science, including

[2]The Mishel Uncertainty in Illness Scale, based on a theory of uncertainty in illness, helps to measure "uncertainty in symptomatology, diagnosis, treatment, relationship with caregivers, and planning for the future" (Mishel, 1981, p. 258).

- Technology that can support self-monitoring and self-management;
- Brain-behavior links and potential environment moderators of successful self-management;
- Interventions to support the self-management of symptoms across chronic conditions;
- Strategies to increase the sustainability of self-management interventions across the lifespan;
- Factors that facilitate the translation of interventions into clinical practice;
- Modifiable epigenetic factors that are influenced by self-management interventions and how they may shape biological and behavioral outcomes; and
- Community interventions to reduce disparities and support self-management in rural and underserved areas (NINR, 2015).

END-OF-LIFE CARE

The IOM report *Dying in America* is largely generalizable to women with ovarian cancer in the late stages of their disease, in that the target group for that report is patients with "a serious illness or medical condition who may be approaching death" (IOM, 2015, p. 1). The report recommends that all stakeholders (including patients and their families, policy makers, clinicians, leaders in health care delivery and financing, researchers, funders, religious and community leaders, advocates, journalists, and members of the public) learn what constitutes good care for people nearing the end of life. Other recommendations that are generalizable to women with ovarian cancer include (1) to assess the woman's physical, emotional, social, and spiritual well-being frequently; (2) to pay attention to physical symptoms, emotional distress, family support, social needs, and spiritual and religious needs; (3) to offer referral to expert-level palliative care; and (4) to offer referral to hospice if the patient has a prognosis of 6 months or less. The following sections describe some of the literature that is specific to end-of-life care for women with gynecologic cancers.

Hospice Care

Hospice care is a specialized end-of-life service, most often covered by the Medicare Hospice Benefit, which is available to patients with a prognosis of 6 months or less who are no longer pursuing anticancer therapy. Retrospective data in non-gynecologic cancers suggest that hospice care is associated with no decrease in the length of survival and an improved length of survival in some cancers and that family members of hospice patients are more likely to report better qualify of life, lower rates of physical

and psychosocial distress, and better quality of death for their loved ones than patients treated in the hospital at the end of life (Connor et al., 2007; Teno et al., 2004; Wright et al., 2010).

In one study of women with recurrent gynecologic cancer, the median overall survival for patients using hospice care was 17 months, compared with 9 months for the group not using hospice (Keyser et al., 2010). Various studies suggest that between 20 and 60 percent of patients who die of ovarian cancer use hospice (Fairfield et al., 2012; Lewin et al., 2005; Lopez-Acevedo et al., 2013a; von Gruenigen et al., 2008; Wright et al., 2014). Other studies show that between 3.5 and 12.1 percent of women with ovarian cancer enroll in hospice in the last 3 days of life (an indicator of poor-quality end-of-life care) (Brown et al., 2014; Fairfield et al., 2012; Lopez-Acevedo et al., 2013a; von Gruenigen et al., 2008). Gynecologic oncology patients are more likely to use hospice services and reap the benefits for themselves and their families when hospice is recommended by their oncology team (Brown et al., 2014).

Barriers to timely hospice use include physicians overestimating how long a patient will likely live and both physicians and patients and their families not being aware of or misunderstanding the benefits of hospice care (Christakis and Iwashyna, 2000; Friedman et al., 2002; Gazelle, 2007; Glare et al., 2003). The requirement that patients forego anticancer therapy in order to enroll in hospice also is a barrier to hospice use, particularly with the recent growth of targeted anticancer therapies with fewer side effects (Lopez-Acevedo et al., 2013b).

Advance Care Planning

According to the IOM report *Dying in America*, "[A]dvance care planning refers to the whole process of discussion of end-of-life care, clarification of related values and goals, and embodiment of preferences through written documents and medical orders" (IOM, 2015, p. 122). Such conversations between providers and women with ovarian cancer are best not left until the point where it is being considered or recommended that the anticancer therapy be discontinued. Oncologists and other providers can contribute to the quality of end-of-life care by having conversations about patients' goals and preferences earlier and often throughout the disease course (Lopez-Acevedo et al., 2013a; Wright et al., 2014). Such conversations have been associated with improved clinical outcomes, including improved patient quality of life, less aggressive medical care near death, earlier hospice referrals, and a reduction in both surrogate distress and costs, and they have not been associated with increased anxiety or depression or loss of hope (Bernacki et al., 2014; Fried et al., 2003; Wright et al., 2008).

Studies of conversations about advanced care planning or the goals of care that include women with ovarian cancer tend to focus on conversations specific to end-of-life care. For example, in a study of admissions of gynecologic oncology patients that resulted in the patient being discharged to a hospice, patients who had had an outpatient discussion about hospice care prior to hospital admission had shorter lengths of stay and were more likely to receive palliative care consultation (Doll et al., 2013). Another study of women who eventually died of ovarian cancer found that 80 percent had a documented conversation about end-of-life care before their death, but those conversations occurred a median of 29 days prior to death (Lopez-Acevedo et al., 2013a). The researchers found that women who had a conversation about end-of-life care at least 30 days before death had less aggressive interventions at the end of life (e.g., less chemotherapy within 14 days of death, lower rates of hospitalization during the last 30 days of life, lower rates of intensive care unit admission during last 30 days of life, and lower rates of admission to hospice within 3 days of death).

Provider Training in Palliative and End-of-Life Care

Gynecologic oncologists are not being well trained in palliative care (Ramondetta et al., 2004). A survey of gynecologic oncology fellows found that while 89 percent felt that palliative and end-of-life care were integral to their training, only 11 percent reported having such training (Lesnock et al., 2013). They also reported that the quantity and quality of training in palliative care was lower than training in other common procedural and oncologic issues. In a separate survey of both gynecologic oncology fellows and candidate members of the SGO, only about 8 percent reported having received formal training (Eskander et al., 2014). A survey of gynecologic oncology fellowship directors found that all reported that their programs had covered at least one palliative care topic in didactic sessions in the previous year and that 48 percent offered a required or elective palliative care rotation, but that only 14 percent had a written palliative care curriculum (Lefkowits et al., 2014). A recent SGO white paper on palliative care suggested that "the SGO should be at the forefront of developing both [palliative care] curricula for our trainees as well as continuing education for current gynecologic oncologists" (Landrum et al., 2015).

KEY FINDINGS AND CONCLUSIONS

The committee offers the following findings and conclusions:

- Most ovarian cancer research focuses on treatment, not supportive care issues.

- Much of the research on survivorship aggregates individuals with different types of cancer, including both gynecologic and non-gynecologic cancers.
- Research specific to survivors of ovarian cancer rarely distinguishes between the needs of older and younger women, of women from different racial and ethnic groups, or of women who have been diagnosed at different stages of disease.
- Retrospective studies may neglect the experiences of women who did not have long-term survival.
- Prospective studies are needed on women starting from initial diagnosis in order to determine issues that are particularly relevant to ovarian cancer and to how survivorship changes over time.
- More research is needed on risk factors for specific physical or psychosocial effects.
- More research is needed on how both health care providers and women themselves can better manage the physical and psychosocial effects of treatment, as well as on how health care providers and others can intervene to help women better self-manage their symptoms.
- Providers need to assess physical and psychological symptoms throughout the care continuum.
- Women with ovarian cancer often undergo active treatment until the end of their lives; both women and their providers need a better understanding of quality-of-life issues in order to determine the benefits of continued treatment versus transitioning to end-of-life care.
- As is the case with other cancers, ovarian cancer care is seldom integrated with palliative care, and gynecologic oncologists may need more training in palliative and end-of-life care.

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6

Recommendations

This report has provided a broad overview of the state of the science in ovarian cancer research, highlighting the major gaps in knowledge and the research challenges that may impede progress in preventing, detecting, and treating ovarian cancers. In assessing the evidence base, the committee focused its attention on identifying the particular research gaps that, if addressed, could have the greatest impact on reducing morbidity or mortality from ovarian cancer for the largest number of women. The committee identified four overarching concepts that should be applied to each recommendation in this report:

- Because high-grade serous carcinoma (HGSC) is the most common and lethal subtype ovarian cancer, its study needs to be prioritized;
- Even with a focus on HGSC, more subtype-specific research is also needed to further define the differences among the various subtypes;
- Given the relative rarity and heterogeneity of ovarian cancers, collaborative research (including the pooling and sharing of data and biospecimen resources, such as through consortia) is essential; and
- The dissemination of new knowledge and the implementation of evidence-based interventions and practices are the final steps in the knowledge translation process. (See Chapter 7.)

The following sections summarize the findings and conclusions of the previous chapters and outline the committee's final recommendations across the spectrum of ovarian cancer research. The committee stresses that these

recommendations need to be considered simultaneously, not sequentially. The recommendations are often intertwined, and the sequence of their presentation here should not be considered as indicative of the priority of their importance or of the necessary order of their implementation.

THE BIOLOGY OF OVARIAN CANCER

As was noted earlier in this report, "ovarian cancer" is a generic term that can be used for any cancer involving the ovaries, but the term is a misnomer in the sense that ovarian cancer is not just one disease. The committee concludes that the term "ovarian cancer" refers to a constellation of several distinct types of cancer involving the ovary. Ovarian cancers can arise from many cell types, and even among ovarian carcinomas there are a number of distinct subtypes. For example, recent evidence suggests that many ovarian carcinomas do not arise in the ovary per se. Instead, these carcinomas may, in fact, arise in other tissues such as the fallopian tubes or ectopic endometrial-type tissue (e.g., endometriosis) and then metastasize to the ovary, or else arise from cells that are not considered intrinsic to the ovary (Brinton et al., 2005; DePriest et al., 1992; Erzen et al., 2001; Forte et al., 2014; Fujii et al., 2014; Kerr et al., 2013; Kindelberger et al., 2007; Kuhn et al., 2012; Kurman et al., 2011; Lee et al., 2006; Pavone and Lyttle, 2015; Przybycin et al., 2010; Robey and Silva, 1989; Rossing et al., 2008; Sainz de la Cuesta et al., 1996; Yoshikawa et al., 2000) (see Figure 2-1). The committee concludes that a substantial proportion of carcinomas labeled "ovarian" may actually originate outside the ovary or arise from cells that are not considered intrinsic to the ovary.

In addition to not having a complete understanding of the sites of origin for ovarian carcinomas, researchers do not have a complete understanding of the pathogenesis of the various subtypes or of the effects of the microenvironment on disease progression. Without better model systems that replicate the manifestations of the human disease, the answers to many key questions will remain elusive. This research gap is further complicated by the significant degree of heterogeneity in ovarian carcinomas, including within and between subtypes. And while the subtypes are distinct, clinicians and researchers tend to combine them in many types of research. The committee concludes that an incomplete understanding of the basic biology of each subtype, especially its origin and pathogenesis, is an impediment to advances in prevention, screening and early detection, diagnosis, treatment, and supportive care. Therefore, the committee recommends the following:

RECOMMENDATION 1: Researchers and funding organizations should design and prioritize preclinical, clinical, and population-based research agendas that take into account the different ovarian cancer

subtypes. A top priority should be elucidating the cellular origins and pathogenesis of each subtype. Particular attention should be paid to:

- **Tumor characteristics such as microenvironment, intratumoral heterogeneity, and progression pathways;**
- **The development of experimental model systems that reflect ovarian cancer heterogeneity; and**
- **Incorporation of the multi-subtype paradigm into prevention, screening, diagnosis, and treatment research.**

The committee re-emphasizes that the subsequent recommendations need to be interpreted in the context of the importance of understanding the distinct issues for each ovarian cancer subtype. However, the committee notes that in research that examines the individual subtypes of ovarian cancer, the rarity of cases of ovarian cancer overall limits the power of individual epidemiologic and treatment studies to draw accurate conclusions. Therefore, the use of consortia and the leveraging of existing data in pooled studies will be important for all types of studies in ovarian cancer. It will be necessary to develop the infrastructure to support such consortia, including data harmonization and the development of new statistical methods.

While it will be critical to apply this multi-subtype approach to research on ovarian cancer, an incomplete understanding of the biology of these cancers has prevented the emergence of uniform standards for describing the disease characteristics for each of the subtypes. Tumor classification, nomenclature, and grading systems have changed over time as new insights have emerged (Gurung et al., 2013; Kalloger et al., 2011; Shih and Kurman, 2004), and evidence suggests that there is great variability in current surgical and pathological practices for the reporting of ovarian cancers and that critical details are missing in a large percentage of reports (Donahoe et al., 2012; Gogoi et al., 2012; Verleye et al., 2011). The committee concludes that the implementation of a single, uniformly implemented nomenclature and classification scheme (with standardized diagnostic criteria) is essential and will serve as the necessary foundation for all future research in ovarian cancer, including treatment course determination. Therefore, the committee recommends the following:

RECOMMENDATION 2: Pathology organizations, oncology professional groups, and ovarian cancer researchers should reach consensus on diagnostic criteria, nomenclature, and classification schemes that reflect the morphological and molecular heterogeneity of ovarian cancers, and they should promote the universal adoption of a standardized taxonomy.

Achieving this consensus will be complex, in part because this process cannot be static. Multiple stakeholders will need to be engaged in an

iterative process in which the schemes can change as new evidence comes to light. Stakeholders can employ a variety of options for moving toward consensus, including the convening of experts to reach consensus on taxonomy or the creation of ongoing working groups by subtype. For example, in 2003 a workshop was co-convened by the National Institutes of Health Office of Rare Diseases, the National Cancer Institute's (NCI's) Office of Women's Health, and the NCI Cancer Diagnosis Program to resolve conflicts regarding the characterization of borderline ovarian tumors (BOTs) (Berman, 2004). In an editorial about the workshop, Berman noted

> In the past several years, pathologists have urged a BOT workshop, expressing the opinion that agreement could be reached on some issues that will help pathologists diagnose BOTs with higher consistency and that will guide clinicians toward a treatment commensurate with the expected clinical behavior of BOTs. For those areas where there is no agreement, a group would seek to develop a commonly accepted way of describing the basis of disagreement. By providing a thoughtful discussion of areas that lack agreement, new areas for future BOT research could be developed. (Berman, 2004)

Another example from a different field is the Lower Anogenital Squamous Terminology project, a consensus-based process co-sponsored by the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology to resolve concerns about multiple diagnostic terms being used by different specialties for human papillomavirus–associated squamous lesions of the lower anogenital tract (Darragh et al., 2013). This consensus process had multiple working groups to address the histopathologic nomenclature for these lesions and sought to "recommend terminology unified across lower anogenital sites" (Darragh et al., 2013, p. 1266). These two efforts—and others like them—can serve as examples for convening multiple stakeholders to reach consensus on taxonomy. Given the complexity of the multiple subtypes of ovarian cancer, such efforts will likely need to occur by subtype or other convention by which the overall taxonomy could be addressed.

The committee again stresses that these first two recommendations about biology research and taxonomy need to be considered simultaneously, not sequentially. That is, a common taxonomy is needed based on the best currently available research, and research designs going forward will need to be based on this common taxonomy, but the taxonomy will also need to evolve as more is learned about the biology of the subtypes. For example, an improved understanding of the molecular characterizations (see Recommendation 8) may, in fact, be more informative for classification than shared appearance. Simultaneously, an enhanced understanding of the characterizations of the subtypes will inform the development of targeted

therapeutics (see Recommendation 9). And, as a further example of the interconnection among this report's recommendations, while Recommendation 9 calls for research on immunologic and molecularly driven treatment approaches, more basic research is needed to understand the immunologic and molecular characteristics of the individual ovarian cancer subtypes in order to drive the development of such novel therapeutics.

RISK ASSESSMENT, SCREENING, AND EARLY DETECTION

Better methods for identifying high-risk women could facilitate the prevention or early detection of ovarian cancers. A family history of ovarian cancer and specific germline (inherited) genetic mutations and hereditary cancer syndromes have strong associations with risk for ovarian cancer (Jervis et al., 2014; Shulman and Dungan, 2010; Soegaard et al., 2009; Stratton et al., 1998; Werness and Eltabbakh, 2001). The *BRCA1* and *BRCA2* genes are the most recognizable ovarian cancer risk–related genes, followed by the mismatch repair genes associated with Lynch syndrome. Several other genes have been identified but are less well studied (Hampel et al., 2015; Hendriks et al., 2006; Lu and Daniels, 2013; Shulman, 2010). Although family history is linked to an increased risk for all ovarian cancer subtypes, it is most strongly linked with risk for HGSC, where up to 25 percent of women have a germline genetic mutation (most commonly in *BRCA1* or *BRCA2*) (Schrader et al., 2012; Walsh et al., 2011). Multiple professional groups recommend that all women diagnosed with an invasive ovarian cancer receive genetic testing and counseling with a cancer genetics professional for a variety of reasons, including to determine appropriate therapies, assess other health risks, and determine the risk for family members (ACS, 2012; Hampel et al., 2015; Lancaster et al., 2015; NCCN, 2015). Genetic counseling and testing are also recommended for the first-degree relatives of women with a hereditary cancer syndrome or germline mutation (i.e., cascade testing). For the first-degree relatives of women with ovarian cancer who have not had genetic testing, genetic counseling would be appropriate for assessing risk and the potential need for testing. Women without ovarian cancer who carry germline mutations associated with greatly increased risk for developing ovarian cancer (sometimes referred to as "previvors") can benefit from enhanced screening, risk-reducing procedures, or chemoprevention (Leonarczyk and Mawn, 2015). However, referrals for genetic counseling and testing are hindered by various patient-, provider-, and system-level barriers, such as a patient's lack of awareness of her family history, the limited time that providers generally have to collect a family history, and complex and inconsistent referral criteria (Hampel et al., 2015). Furthermore, more research is needed to determine the significance

of known mutations and to discover new significant mutations for all subtypes. Therefore, the committee recommends the following:

RECOMMENDATION 3: Researchers, public health practitioners, and clinicians should develop and implement innovative strategies to increase genetic counseling and testing as well as cascade testing for known germline genetic predispositions in appropriate populations (e.g., untested ovarian cancer survivors and relatives of individuals who tested positive). Furthermore, researchers, clinicians, and commercial laboratories should determine the analytic performance and clinical utility of testing for other germline mutations beyond *BRCA1* and *BRCA2* and the mismatch repair genes associated with Lynch syndrome.

The committee recognizes that relying on family history alone may lead clinicians to overlook some women with germline mutations that put them at higher risk for ovarian cancer. Up to one-half of women with high-risk germline mutations do not have an apparent family history of breast or ovarian cancer (Schrader et al., 2012; Walsh et al., 2011). Also, family history may not identify high risk for women with few female relatives, for women who were adopted and do not know their biological family's cancer history, or for women who otherwise do not know the family health history of one or both parents. (Lancaster et al., 2015).

Furthermore, as the majority of women with an ovarian cancer do not appear to have a known high-risk germline mutation or a significant family history, it is critical to also consider other potential risk factors. While several nongenetic factors are associated with either an increased or a decreased risk for developing ovarian cancers (see Table 3-1), the patterns of association are inconsistent. For example, some risk factors may affect risk in the same way for all subtypes, whereas other factors may increase risk for some subtypes while decreasing risk for other subtypes. The strongest known risk factors to date are those associated with the less common and less lethal subtypes. Therefore, the committee recommends the following:

RECOMMENDATION 4: Researchers and funding organizations should identify and evaluate the underlying mechanisms of both new and established risk factors for ovarian cancers in order to develop and validate a dynamic risk assessment tool accounting for the various ovarian cancer subtypes. Furthermore, a spectrum of risk factors should be considered, including genetics, hormonal and other biological markers, behavioral and social factors, and environmental exposures.

Collaborations between clinicians and population and basic scientists will help identify potential new risk factors and also provide an opportunity

to better understand how specific exposures influence disease development. Current research does not provide insight into which risk factors need to be prioritized for future research. In light of the heterogeneity of the cell of origin, an emphasis on factors that influence early carcinogenesis may have the largest impact on identifying women at high risk. Furthermore, consortia will be again needed in order to provide sufficient power to evaluate potential risk factors, particularly for the less common subtypes and rare exposures.

Women known to be at high risk may benefit from surgical and nonsurgical preventive measures, but the risk–benefit ratios of these measures need to be better defined for different tumor subtypes and at-risk populations. For example, risk-reducing surgeries (e.g., bilateral salpingo-oophorectomy and salpingectomy) and the use of prescription medications (e.g., oral contraceptives) need to be weighed against potential complications and long-term side effects (e.g., stroke risk, risk for other cancers, surgical complications, and overall mortality) (Bassuk and Manson, 2015; Beral et al., 2008; Cibula et al., 2011; Daly et al., 2015; Evans et al., 2009; Falconer et al., 2015; Finch et al., 2014; Guldberg et al., 2013; Havrilesky et al., 2013; Madsen et al., 2015; McAlpine et al., 2014; Nelson et al., 2014; Walker et al., 2015). As new prevention strategies are developed, researchers will need to amass an evidence base for their efficacy as well as their potential long-term harm. Collaborative research and longitudinal sampling will again be important when performing these types of studies, especially in the determination of the long-term impact of these interventions..The committee concludes that much remains to be learned about risk assessment and prevention strategies for specific subtypes and in specific populations. Therefore, the committee recommends the following:

RECOMMENDATION 5: Clinicians, researchers, and funding organizations should focus on quantifying the risk–benefit balance of nonsurgical and surgical prevention strategies for specific subtypes and at-risk populations.

Better methods for identifying high-risk women would likely affect the morbidity and mortality of ovarian cancer by helping to prevent or detect ovarian cancers as early as possible. Current approaches for early detection include assaying for biomarkers (e.g., CA-125), often in combination with imaging technologies. While the use of these strategies in large screening trials has resulted in more ovarian cancers being detected at earlier stages, to date these methods have not had a substantial impact on overall mortality (Buys et al., 2011; Jacobs et al., 2015; Kobayashi et al., 2008; Menon et al., 2015; van Nagell et al., 2007). Given the marked heterogeneity of ovarian cancers and the incomplete understanding of early disease devel-

opment for each subtype, it is highly unlikely that a single biomarker or imaging modality will be sufficient to aid in the early detection of all the subtypes. The committee concludes that current screening strategies have not had a substantial impact on reducing mortality in the general population and that while research on refining current methods may be fruitful, distinct multimodal approaches will likely be needed to detect each of the various subtypes at their earliest stages. Therefore, the committee recommends the following:

RECOMMENDATION 6: Researchers and funding organizations should focus on the development and assessment of early detection strategies that extend beyond current imaging modalities and biomarkers and that reflect the pathobiology of each ovarian cancer subtype.

Going forward, screening trials may be more informative if conducted in populations with elevated ovarian cancer risk. Trials could be conducted in populations of women identified to be at high genetic risk and also in high-risk populations that are newly identified as a result of using the risk assessment tool from Recommendation 4. Research on the impact of earlier detection on quality of life will also be important.

DIAGNOSIS AND TREATMENT

Compared to the situation over the past few decades, newly diagnosed ovarian cancers are now being more accurately and consistently staged. Thanks both to better characterization of tumor biology and to a precision medicine approach in the development of therapeutics, a wider variety of treatment options now exist. Most women with newly diagnosed ovarian cancer undergo primary debulking surgery (PDS) to remove as much of the grossly visible tumor as possible (cytoreduction) as well as to make it possible to determine a specific diagnosis (e.g., subtype, staging). Progression-free survival and overall survival are markedly better for women who have complete (or optimal) tumor resection, yet great variability exists in the extent of tumor resection (Chi et al., 2012; du Bois et al., 2009; Hacker, 2013). For women in whom an optimal resection is not thought to be feasible or who are unable to undergo PDS due to comorbidities, neoadjuvant chemotherapy (NACT) can reduce tumor burden and facilitate subsequent resection (Morrison et al., 2012; Vergote et al., 2013). After surgery, women typically receive multiple cycles of chemotherapy.

While the majority of women respond well to initial treatment, most will experience a recurrence of the disease (Coleman et al., 2013), resulting in cycles of repeated surgeries and additional rounds of chemotherapy. Women with recurrent disease have better outcomes when all grossly visible

tumor is removed during the subsequent surgical resections (Al Rawahi et al., 2013; Harter et al., 2006).

Standard of Care

Several organizations have developed standards of care for the assessment and treatment of women with both newly diagnosed and recurrent ovarian cancers. Women who receive care in accordance with National Comprehensive Cancer Network (NCCN) clinical practice guidelines have considerably better clinical outcomes (e.g., improved survival and fewer surgical complications) than patients who do not receive the standard of care (Bristow et al., 2013b; Chan et al., 2007; Eisenkop et al., 1992; Goff, 2015). However, less than half of women with ovarian cancer nationwide receive care that adheres to NCCN guidelines (Cliby et al., 2015). For example, while the intraperitoneal (IP) route for the delivery of chemotherapy offers notable advantages over intravenous (IV) and oral routes, the adoption of IP chemotherapy protocols is not widespread (Armstrong et al., 2006; Hess et al., 2007; Jaaback et al., 2011; Tewari et al., 2015). However, this is due in part to concerns regarding the efficacy and potential adverse effects of IP administration, and the better side-effects profile associated with newer IV regimens (Katsumata et al., 2009; Wright et al., 2015).

In addition to the variation in adherence to standards of care for surgery and chemotherapy, the guidelines for cancer genetics referrals are not routinely or widely implemented at this time (see Recommendation 3) (Febbraro et al., 2015; HHS, 2013; Powell et al., 2013). Testing for germline genetic mutations among women already diagnosed with ovarian cancer is important because the presence of certain mutations informs the decision-making process and helps clinicians determine the most appropriate therapy.

Being treated by a gynecologic oncologist and having treatment in a high-volume (often urban) instead of a low-volume (often rural) hospital or cancer center are the two most significant predictors of whether a woman with ovarian cancer will receive the standard of care, and both are associated with better outcomes (Bristow et al., 2013a, 2014). Significant predictors of nonadherence to the standard of care include the patient being of advanced age at diagnosis, having one or more treatment-limiting comorbidities, being of a non-white race, and having a lower socioeconomic status (Bristow et al., 2013a,b; Chase et al., 2012; Du et al., 2008; Erickson et al., 2014; Goff et al., 2007; Harlan et al., 2003; Howell et al., 2013; Jordan et al., 2013; Joslin et al., 2014; Thrall, 2011). Like most other cancers, ovarian cancer primarily affects older adults, but little is known about the care needs of older women with ovarian cancer. For example, older women are more likely to have comorbidities that may

preclude them from receiving care in accordance with NCCN guidelines, which, in turn, may lead to worse outcomes. In addition to the disparities in how care is delivered, historical trends show considerable differences in outcomes by race (Howlader et al., 2015). Furthermore, some studies show geographic variations in the patterns of cancer care, which may be due to socioeconomic or other factors (Fairfield et al., 2010; Polsky et al., 2006; Ulanday et al., 2014). Finally, more research is needed on how quality metrics can be used to help promote the delivery of the standard of care. The committee concludes that the current patterns of care for women with newly diagnosed and recurrent ovarian cancers reveal inconsistencies in therapeutic approaches and disparities in care and subsequent outcomes. Therefore, the committee recommends the following:

RECOMMENDATION 7: To reduce disparities in health care delivery and outcomes, clinicians and researchers should investigate methods to ensure the consistent implementation of current standards of care (e.g., access to specialist care, surgical management, chemotherapy regimen and route of administration, and universal genetic germline testing for newly diagnosed women) that are linked to quality metrics.

In order to meet the standard of care, no one model of care will serve all patients in all settings. For example, women in rural settings may not have access to a gynecologic oncologist or a high-volume cancer center. Therefore, it will be necessary to explore alternative models of care that may help to meet the standard of care, such as the use of telemedicine for consultation and the use of patient navigation systems to allow women to be more engaged in their own care. The committee recognizes that, as is the case in other areas of health care, changes in payment, policy, education and training, and other areas will likely be needed to effectively implement these models of care.

Predicting Response

While adherence to standards of care leads to improved outcomes, little is known about why some women respond better to specific surgical and chemotherapeutic therapies or about how age affects treatment. For example, some research shows that PDS and NACT have similar outcomes, but these studies have come under criticism for their study design (Dai-yuan et al., 2013; Hacker, 2013; Vergote et al., 2010). As such, the question of which women should receive initial PDS or NACT remains unresolved. It may be that women with certain subtypes respond better to different therapies or that women who respond particularly well to a given treatment may share characteristics that extend beyond their tumor subtype.

Current classification systems also do not, for the most part, help to tailor treatment regimens. For women with recurrent disease, the traditional classification system of platinum sensitive or platinum resistant does not reflect the improved understanding of recurrent disease, particularly given the ability to diagnose these recurrences at earlier time points, the improved understanding of the impact of *BRCA* mutation status on response to therapy for recurrence, and the heterogeneous response noted in patients with platinum-resistant tumors (Davis et al., 2014; Guth et al., 2010). Several assays have been developed (or are in development) to determine the likelihood of primary and recurrent tumors' ability to respond to various chemotherapeutic agents, but at this time none of them have been validated (Rutherford et al., 2013). Therefore, the committee recommends the following:

RECOMMENDATION 8: Clinicians and researchers should focus on improving current treatment strategies, including

- **The development and validation of comprehensive clinical, histopathologic, and molecular characterizations that better inform precision medicine approaches for women with newly diagnosed and recurrent disease;**
- **Advancement in the understanding of the mechanisms of recurrent and drug-resistant (e.g., platinum-resistant) disease and the development of a more informative classification system;**
- **The identification of predictors of response to therapy and near-term indicators of efficacy; and**
- **The determination of the optimal type and timing of surgery in women newly diagnosed with ovarian cancer and of the efficacy of subsequent cytoreduction procedures for women with recurrent disease.**

Improvements in the clinical, histopathologic, and molecular characterizations of tumors will help inform the iterative process of developing the standardized taxonomy (see Recommendation 2). Furthermore, this improved understanding may help to improve outcomes, as certain characterizations may help clinicians to determine which women are more likely to have positive outcomes, or which treatments are most likely to be beneficial. Several modalities can be used to match individual patients to specific procedures and treatments. The analysis of biomarkers, the determination of the molecular features of tumors, minimally invasive assessments (e.g., laparoscopy), and the use of imaging all provide insights. Furthermore, a variety of approaches can be used to predict therapeutic efficacy, including scoring systems, genetic germline testing, and molecular profiling. For example, the committee notes that trials in other cancers commonly rec-

ommend tumor biopsy to better direct recurrent disease treatment. The knowledge gained through these precision medicine approaches will also help to inform the development of new and better treatments.

Developing Better Treatments

While clinicians need better ways to select the appropriate among existing treatments for individual patients, they also need more treatment options, and the development of better treatments depends in large part on the clinical trials system. The 2010 Institute of Medicine (IOM) report *A National Cancer Clinical Trials System for the 21st Century* noted that individual companies may have less incentive to conduct studies to compare the effectiveness of treatment options, combine novel therapies developed by different sponsors, test multimodality strategies, or develop therapies for rare diseases (IOM, 2010). The report outlined goals and recommendations to improve the clinical trials system in general, including

- Streamline and harmonize government oversight (e.g., U.S. Food and Drug Administration regulations);
- Improve collaboration among stakeholders, including through the use of consortia;
- Define an effective mechanism for combining products in clinical trials;
- Develop and evaluate novel trial designs;
- Increase the accrual volume, diversity, and speed of clinical trials; and
- Educate patients about the availability, payment coverage, and value of clinical trials.

These principles are particularly relevant for translational research in ovarian cancer, given the relative rarity of the disease combined with the diversity of subtypes. Comparative effectiveness studies, combination therapies, and multimodality strategies will all be important to reducing morbidity and mortality in ovarian cancer. Therefore, this committee endorses these goals and recommendations and suggests that these principles be applied to all recommendations of this report related to clinical trials for ovarian cancer research.

Clinicians currently have limited options for drug therapy, and the long-term efficacy of these agents is limited by a high rate of drug resistance. A better understanding of the histologic subtypes and molecular features of the range of ovarian cancers has led to a more targeted approach for the use and development of new therapeutic treatments. To address the growing number of new therapeutics, innovative early phase clinical trials that

incorporate biomarkers predictive of efficacy are needed to help identify which ovarian cancer histologic and molecular subtypes are likely to be resistant or responsive to specific new therapies.

However, selecting clinically meaningful endpoints for trials in ovarian cancer can be challenging. For example, it may be difficult to determine the impact of a single agent on overall survival because women typically have had multiple previous therapies. Patient preferences also need to be considered in assessing the effectiveness of new therapies (e.g., what level of side effects is considered tolerable for a woman, given the expected improvement in outcomes associated with a new drug). Yet another issue is that little research has been done on nonpharmacologic therapies and interventions (e.g., diet, exercise, stress reduction) that might affect response to treatment. Overall, the committee concludes that the current standard of care lacks precision medicine approaches to therapy. Therefore, the committee recommends the following:

RECOMMENDATION 9: Researchers should develop more effective pharmacologic and nonpharmacologic therapies and combinations of therapies that take into account the unique biology and clinical course of ovarian cancer. These approaches should include

- **Developing immunologic and molecularly driven treatment approaches specific to the different ovarian cancer subtypes;**
- **Identifying markers of therapeutic resistance and exceptional response; and**
- **Using interdisciplinary teams to design and conduct statistically efficient and information-rich clinical studies.**

The development of new immunologic and molecularly driven treatment approaches depends largely on improving our understanding of the immunologic and molecular characteristics of ovarian cancer at a basic science level (see Recommendation 1). However, research on such newer treatment options is once again complicated by the relative rarity of the disease overall and by the heterogeneity of the subtypes. As the committee did not find evidence for the superiority of any single treatment, it concluded that a variety of approaches need to be evaluated, including new combinations of existing drugs, new drug formulations, targeted biologics, protein inhibitors, TP53-directed therapies, anti-angiogenics, immunotherapies, and nonpharmacologic interventions. All of these approaches have merit because their effectiveness may vary within and among subtypes.

SUPPORTIVE CARE ALONG THE SURVIVORSHIP TRAJECTORY

Most research on ovarian cancer focuses on the treatment of the disease rather than on how to improve the management of the acute and long-term physical and psychosocial effects of diagnosis and treatment across the trajectory of survivorship. Although research on therapies that may provide life-saving benefit is obviously crucial, complementary research on how to best support women living with ovarian cancer and improve their quality of life is also important for them and their families. Women with ovarian cancer, even those with recurrent disease, often live many years following diagnosis. These women require early and ongoing supportive care to ensure that aggressive, life-extending treatments are enhanced by multidisciplinary supportive care to maximize quality of life.

A 2013 IOM report stated, "A high-quality cancer care delivery system depends upon clinical research that gathers evidence of the benefits and harms of various treatment options so that patients, in consultation with their clinicians, can make treatment decisions that are consistent with their needs, values, and preferences" (IOM, 2013, p. 207). However, for women diagnosed with ovarian cancer, shared decision making and the management of the physical and psychosocial effects of diagnosis and treatment may be neglected in the effort to urgently address the primary disease, which is typically at an advanced stage at diagnosis. Also, a lack of professional expertise or resources may hinder joint decision making.

Current research provides little insight as to which women are most likely to suffer physical and psychosocial effects as a result of their diagnosis and treatment or on the best approaches for managing these effects. Furthermore, there may be differences in the needs of and best approaches for women of different demographic groups (e.g., older versus younger women and women in different racial and ethnic groups). Traditionally, the systematic assessment of symptoms and quality of life in ovarian cancer has not been a major focus in clinical practice. In 2010, the IOM called on the Patient-Centered Outcomes Research Institute (PCORI)[1] and others to "develop a common set of data elements that captures patient-reported outcomes, relevant patient characteristics, and health behaviors that researchers should collect from randomized clinical trials and observational studies" (IOM, 2009, p. 12). Furthermore, the optimal medical management of treatment side effects requires an iterative approach with in-depth conversations between the patient and her interdisciplinary team of clinicians. Given the current structure of the health care system and the time pressures to move patients through clinics, these types of interactions are

[1]For more information, see http://www.pcori.org (accessed July 22, 2015).

difficult to achieve. Approaches to enhancing self-management, including leveraging mobile health technologies, need to be explored.

Research gaps may in part be addressed by more effective clinical assessment of patient-reported symptoms and outcomes during treatment, especially the outcomes that are most important to women with ovarian cancer (e.g., improved quality of life versus longer survival). Furthermore, because many women with ovarian cancer continue active treatment until the end of their lives, researchers need to help better define when disease-focused treatments are unlikely to be effective and the focus should shift to high-quality end-of-life care. The committee concludes that a majority of women with ovarian cancer require long-term active disease management, necessitating more effective approaches for supportive care and self-management across the survivorship trajectory. Therefore, the committee recommends the following:

RECOMMENDATION 10: Researchers and funding organizations should study the supportive care needs of patients with ovarian cancer throughout the disease trajectory, including

- **Identifying the array of factors that put women at high risk for poor physical and psychosocial outcomes;**
- **Identifying and overcoming barriers to the systematic assessment of the physical and psychosocial effects of disease and treatment;**
- **Developing and implementing more effective supportive care and self-management interventions; and**
- **Defining the parameters that indicate when patients and their families would benefit from transitioning to end-of-life care.**

The committee recognizes that many of the supportive care needs of women with ovarian cancer are similar to those of women with other cancers. The committee therefore endorses the following goals and recommendations from previous IOM reports that are relevant to supportive care for women with ovarian cancer:

- Organizations sponsoring research in oncology should include research on the development of reliable, valid, and efficient tools and strategies for use by clinical practices to ensure that all patients with cancer receive care that meets the standard of psychosocial care, including
  - Approaches for improving patient–provider communication and providing decision support to patients;
  - Screening instruments to identify individuals experiencing psychosocial problems;

  - Needs assessment instruments for psychosocial care planning; and
  - Illness and wellness management interventions (IOM, 2008).
- The cancer care team should provide patients and their families with understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of total and out-of-pocket costs of cancer care (IOM, 2013).
- To expand the depth of data available for assessing interventions, stakeholders should build on ongoing efforts to develop a common set of data elements that capture patient-reported outcomes, relevant patient characteristics, and health behaviors that researchers should collect from clinical trials and other studies (IOM, 2013).
- In the setting of advanced cancer, the cancer care team should provide patients with end-of-life care consistent with their needs, values, and preferences. The cancer care team should place a primary emphasis on providing cancer patients with palliative care, psychosocial support, and timely referral to hospice care for end-of-life care (IOM, 2013).
- Stakeholders should provide fact-based information about care of people with advanced serious illness to encourage advance care planning and informed choice based on the needs and values of individuals (IOM, 2015).

DISSEMINATION AND IMPLEMENTATION

Amassing evidence on risk factors, treatments, and preventive strategies is not sufficient to ensure that this knowledge will be acquired and utilized by all stakeholders. A number of factors influence the movement of science into regular and effective use, including the complexity of health care systems, the capacity of practitioners and providers to absorb new knowledge, and the diversity of stakeholders.

A review and discussion on the evidence base of dissemination and implementation science, as well as a discussion of potential avenues for dissemination and implementation of specific messages for women diagnosed with or at risk for ovarian cancer, is presented in the following chapter.

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7

Dissemination and Implementation

The preceding chapters have described a host of findings and conclusions in the field of ovarian cancer research. The scientific evidence behind many of these findings and conclusions is robust and has been published in peer-reviewed scientific journals. This chapter addresses how these findings and conclusions are best translated into useful applications. The final step of translation is to disseminate new information and implement new interventions for multiple audiences and practice settings, whether the individuals are patients, family members, providers, advocates, health systems, payers, or other researchers. In this chapter, an overview of the science of dissemination and implementation (D&I) is presented and then applied to the research on ovarian cancers.

INTRODUCTION

The National Institutes of Health (NIH) Roadmap initiative has been concerned not only with the translation of basic science into applied clinical trials, but also the process of the dissemination (also referred to as knowledge utilization or knowledge integration) of effective interventions into general practice (Zerhouni, 2003). The NIH has recognized that amassing evidence on risk factors, treatments, and preventive strategies is not enough to ensure that this knowledge will be effectively used. Traditionally much effort has been spent on understanding the efficacy and effectiveness of a particular intervention, while not enough has been spent on D&I, the final stage of the translational process (Khoury et al., 2007). A variety of factors must be taken into account when trying to move science into regular

and effective use, including the complexity of multiple health care systems, the capacity of active providers, and the diversity of the target audiences. Anyone involved in the D&I process must also take into account the breadth of different cultures and languages across the United States. It is clear that a "one-size-fits-all" approach will not be sufficient to translate knowledge into practice for all stakeholders. Hence, it is important that all stakeholders engaged in D&I work together to improve the dissemination of important information that can lead to improvements in ovarian cancer outcomes as a whole.

Additional stages of D&I research are needed after efficacy and effectiveness studies to ensure the integration of new knowledge into practice (see Figure 7-1). *Exploration* involves the identification of the audiences for which a broader application of the intervention is desirable or appropriate. *Adoption* involves modifying or tailoring the intervention to fit the needs of a particular target group. *Implementation* refers to integrating the practice or intervention in specific settings. *Sustainment* (or sustainability) involves scaling up the intervention and ensuring its maintenance in organizations and communities.

DISSEMINATION

Dissemination is an active approach of spreading evidence-based interventions to the target audience via determined channels using planned strat-

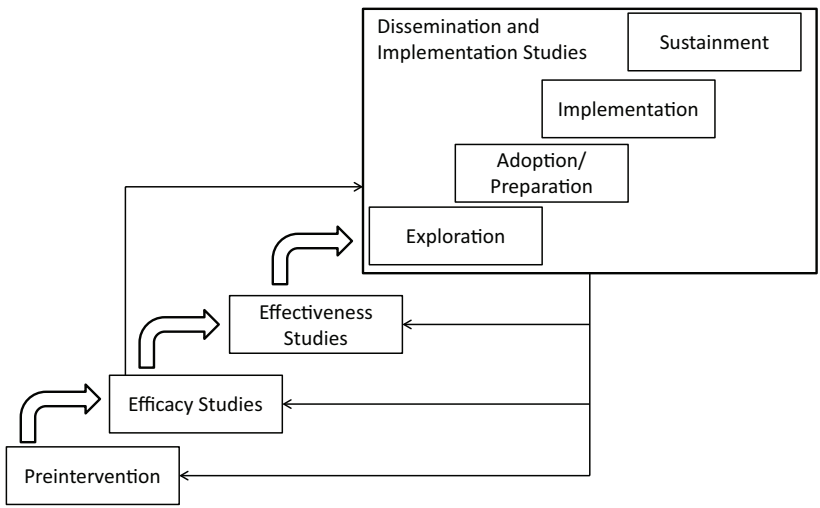

FIGURE 7-1 Stages of research and phases of dissemination and implementation.
SOURCES: Brownson et al., 2012; NRC and IOM, 2009.

egies" (Brownson et al., 2012, p. 26) The process of dissemination involves the packaging and communication of information so that the information can most effectively be transmitted to its target audience (Lomas, 1993).

General Dissemination

The gap between knowledge generation and its application is a challenge for both clinical medicine and public health (Green et al., 2009). The diffusion of novel techniques and practices into general use does not occur spontaneously, and the unaided process is inconsistent and slow (Rogers, 2003). Moving knowledge from discovery to general use requires the active participation of multiple stakeholders (Bero et al., 1998; Bowen et al., 2009). Passive methods of dissemination such as scientific journals, practice guidelines, and mass mailings are not as effective as such methods as personal technical assistance, point-of-decision prompts, and mass media campaigns (Rabin et al., 2006). Furthermore, using individual channels of information generally proves less successful than using multiple sources of messages (Bero et al., 1998; Clancy et al., 2004). Credible sources of information are influential in convincing people to consider new ideas or topics more easily (Smith et al., 2013). However, much of human behavior is shaped by the messages and ideas presented in public health, advertising, and marketing efforts. Therefore, shaping the world's view of a new activity or fact is in part determined by the messaging that can be found in multiple situations and settings.

The process of disseminating information or programs needs to be tailored to the unique characteristics of different audiences (e.g., age, gender, racial and ethnic background, language, and literacy level). Furthermore, readiness for change can be measured at the individual level (e.g., is an individual ready to hear and use new information?) or at an organizational level (e.g., is an organization ready to embrace a new practice or policy?), and the measured level of readiness can guide the approach used in moving the change forward (Johnson et al., 2014; Lewis et al., 2015).

Dissemination in Existing Systems

Such systems as health care organizations, hospitals or networks, workplaces, and schools are multilevel and include complex groups of people organized for a common purpose. Each system has formal and informal elements that present different opportunities and barriers to the dissemination of new or critical products and information. Researchers who seek to understand system change in health care settings have emphasized the importance of two characteristics in particular, organizational culture and climate. *Organizational culture* refers to the characteristics that make an

organization different from other organizations, while *organizational climate* is the general feel and status of the organization or group, and both are important to dissemination of research (Hsu and Marsteller, 2015). Leadership is another critical component of a system that can influence how a new idea is disseminated.

Another important factor in the dissemination of information or programs into systems is *organizational readiness*, which is the state of being ready to change practices or policies based on new or often external input, and represents a combination of the readiness of individuals within the system together with the necessary resources and motivation to enact the changes needed to support the innovation. Yet another factor to consider is that dissemination and innovation incurs costs, and these costs are often unknown at the beginning of the dissemination effort. Concern about costs (e.g., profitability) is one issue described as being prohibitive for the adoption of new knowledge or programs (Dearing and Kreuter, 2010). The Commonwealth Fund has developed eight strategies for systemic approaches to disseminating evidenced-based practices in national campaigns for quality improvement (The Commonwealth Fund, 2010) (see Box 7-1).

BOX 7-1
Effective Strategies for the Dissemination of Evidence-Based Practices

Strategy 1.	Highlight the evidence base and the relative simplicity of recommended practices.
Strategy 2.	Align the campaign with the strategic goals of the adopting organizations.
Strategy 3.	Increase recruitment by integrating opinion leaders into the enrollment process and employing a nodal organizational structure.
Strategy 4.	Form a coalition of credible campaign sponsors.
Strategy 5.	Generate a threshold of participating organizations that maximizes network exchanges.
Strategy 6.	Develop practical implementation tools and guides for key stakeholder groups.
Strategy 7.	Create networks to foster learning opportunities.
Strategy 8.	Incorporate the monitoring and evaluation of milestones and goals.

SOURCE: The Commonwealth Fund, 2010.

Dissemination to Providers

The main avenue of scientific dissemination to clinicians has been the scientific journal article, supplemented by presentations at national meetings and, recently, social media. Forming and publishing guidelines (see later in this chapter) was thought of as a supplemental way to focus providers on the most important ways to understand the literature and incorporate it into practice. However, such guidelines are inadequate for giving health care providers the most relevant and up-to-date information where they need it (Bero et al., 1998; Grimshaw et al., 2001). Proven alternative approaches include reminders (either manual or computerized), interactive educational meetings (e.g., workshops that include discussion or practice), and multifaceted interventions that include two or more of the following: audit and feedback, reminders, local consensus processes, or marketing (Bero et al., 1998). Passive diffusion using audiovisual materials and electronic publications, along with didactic educational meetings, is generally ineffective (Bero et al., 1998).

Enabling strategies are intended to offer providers the information and skills they need to change their practices. For example, the pharmaceutical marketing of new products to providers, also known as *academic detailing*, is an effective and consistent method of increasing provider uptake of new ideas or programs across multiple provider and intervention types (Fischer and Avorn, 2012). This strategy takes a marketing approach for disseminating new knowledge or programs to providers, with a mixture of one-on-one engagement, incentives, and practice consults about new findings, knowledge, or programs that could benefit providers and their patients. Other strategies offer providers the skills necessary for good practice, such as training programs in communication or consultation about a specific topic (e.g., palliative care and bereavement) (Back et al., 2008). Taken together, these methods are useful for changing an individual provider's actions with respect to specific patient situations or types.

Dissemination to Patients and Families

A number of strategies have been used to disseminate health-related information to the general public, including national campaigns, mail, email, and the telephone (Hesse et al., 2010). Because of the increased use of electronic communication methods (e.g., smart phones), newer dissemination methods often use social media outlets and mHealth applications (Subhi et al., 2015). However, misinformation is common in websites, tweets, and other social media platforms, which leads to inaccurate ideas about health and prevention being disseminated to large audiences (Eysenbach et al., 2002).

Another way that information has been disseminated to targeted members of the public is the use of "critical others" who are in contact with the target audience. For example, in one use of a program called the 5 As (Ask, Assess, Advise, Assist, and Arrange), having health care providers deliver smoking cessation message to patients during an office visit resulted in positive outcomes (AHRQ, 2012). Strategies for delivering messages to children often use parents as the delivery system, and families of patients have been targeted as a channel for delivering information and support to those patients (Gavin et al., 2015). These existing communication channels are important social influences for health and can be effective ways to deliver new information to the right targets.

IMPLEMENTATION

Dissemination strategies alone are insufficient to ensure the widespread use of an intervention, and so strategies for implementation are also needed (Dearing and Kreuter, 2010; Shediac-Rizkallah and Bone, 1998). Implementation is "the process of putting to use or integrating evidence-based interventions within a setting" (Brownson et al., 2012, p. 26).

General Implementation

Creating a guideline about a new fact or a finding and then disseminating that guideline to relevant providers is generally not sufficient to bring about a new practice pattern. Many levels of decision and action must change before a system implements a new practice. Knowing that the change must happen is often the first step and is often a key factor for overall change. However, many other elements of the system must change in order to produce sustainable and pervasive change. For example, many of the same variables that affect the dissemination of information in organizations are also likely to affect implementation (e.g., organizational climate, readiness, and culture). Relationships and communication among the relevant stakeholders is critical to successful implementation (Luke and Harris, 2007).

Most systems are continuously adapting to new conditions, regulations, and financing, which requires both push and pull types of change. Technologies that push people to change ("push technologies") work best on a population level when they are directly offered, or pushed, to users. Technologies that users find and use, without any sort of external offer or encouragement are referred to as "pull technologies." Often they are used together to compel as many people as possible to implement a new practice. Innovation and change can also come from top-down approaches, such as with the creation of a central policy that pulls the rest of the organization along with it. However, bottom-up change, where the individuals within

the system identify a problem and implement the change necessary to solve it, can also be a useful means of innovation. Both of these approaches are likely necessary for any organization that wishes to implement appropriate new ideas and programs.

Implementation is particularly complex in the clinical setting for cancer treatment, in part because there are multiple types of providers, each with relevant tasks and input into the treatment process. In the case of ovarian cancer, the gynecologic oncologist is often a key decision maker, but many others are also involved in developing a treatment plan that they all need to implement together. Beyond the oncology specialists, there are usually multiple types of medical providers and offices involved, including pathology and laboratory facilities, primary care teams, supportive care teams, and others. Often each must be involved in decisions about a single patient, and each has a role in supporting the patient through the process of treatment. In the health care setting, effective implementation of new information or interventions also needs patient engagement and involvement, along with input from families and other caregivers. Other important stakeholders include advocacy groups and members of the media, who are often left out of the process until later but are incredibly influential in shaping public opinion.

Conceptual Model of Implementation Research

Conceptual models that guide research on the processes and structures of implementation are still being developed (Tabak et al., 2012). Proctor and colleagues summarized eight processes needed to implement an innovation in a system and introduced the concept of implementation outcomes, as opposed to clinical outcomes, in order to evaluate the success of the implementation efforts themselves (Proctor et al., 2009, 2011). Damschroder and colleagues identified characteristics of the setting and innovation itself that have an impact on the implementation of new ideas into a system (Damschroder et al., 2009). Taken together, these models provide a useful starting place for considering relevant issues for the implementation of new knowledge and interventions by showing the interaction among intervention strategies, implementation strategies, and outcomes (including implementation outcomes, service outcomes, and client outcomes) (Proctor et al., 2009)

Changes in health care administration, organization, and funding may dramatically affect implementation efforts. For example, changes brought about by the Patient Protection and Affordable Care Act[1] could revolutionize access to care, especially in states that opt for Medicaid expansion or

[1]Patient Protection and Affordable Care Act, Public Law 148, 111th Cong., 2nd sess. (March 23, 2010).

other forms of population-wide provision of health care, making lack of access less of a barrier to the delivery of up-to-date information.

READY FOR DISSEMINATION AND IMPLEMENTATION

A confluence of actions is often needed if new knowledge is to be successfully translated into applications in general use. For example, the routine use of mammography for the early detection of breast cancer was implemented when imaging facilities and trained radiologists became sufficiently available, the practice was recommended by multiple guidelines groups, and its costs were paid for by both private and public insurers (Deppen et al., 2012). On the other hand, vaccination against human papillomavirus (HPV) for the prevention of cervical cancer proved highly effective in trials and was recommended for wide use but faced challenges in D&I because of cultural and religious beliefs in certain populations (Greenfield et al., 2015).

When Has an Issue Arrived?

One of the most complex and controversial issues in the D&I process is determining when a product, finding, or intervention is ready to be put into general practice. Individual studies are usually not sufficient. Rather, an accumulation of studies and the replication of findings, often culminating in a rigorous systematic review of the literature, is required. Individual systematic reviews are often conducted by groups of investigators; for example, the Cochrane Collaboration provides a system to summarize evidence and findings from multiple sources (Cochrane, 2015). Several guidelines (e.g., the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines) have been created to assist stakeholders in interpreting the scientific literature and in deciding about the best ways to implement new ideas for practice (Moher et al., 2009).

The guideline review process, as used by the U.S. Preventive Services Task Force and the Community Preventive Services Task Force, makes recommendations about which clinical activities should be put into practice (Community Preventive Services Task Force, 2015; USPSTF, 2015). Clinical practice guidelines are intended to help providers (and patients) make choices about best practices, and adherence to certain guidelines is often used as a measure of the quality of cancer care. Many medical professional groups have processes for creating their own guidelines for care. In ovarian cancer, guidelines exist for screening (e.g., National Society of Genetic Counselors), clinical services (e.g., American College of Obstetricians and Gynecologists, and Society for Gynecologic Oncology), and treatment (e.g., National Comprehensive Cancer Network) (ACOG, 2015; NCCN, 2015;

SGO, 2015). Clinical guidelines for palliative care, such as those developed by the National Consensus Project for Quality Palliative Care, are also applicable to women with ovarian cancer (NCP, 2013). Taken together, these review processes are necessary for deciding what is ready for dissemination.

What Is Already Available?

Providing information about ovarian cancer requires a wide variety of stakeholders, including federal agencies (e.g., the Centers for Disease Control and Prevention [CDC], the U.S. Department of Defense, the U.S. Food and Drug Administration, the NIH), private foundations, industry, academic institutions, professional societies, and advocacy groups. For example, the National Cancer Institute (NCI) provides patient-oriented information about treatment options, the effects of treatment, screening, and active research areas in ovarian cancer treatment and prevention (NCI, 2015). In addition, the NCI website describes genetic mutations and other risk factors that put women at risk for ovarian cancer. The CDC website also provides information on ovarian cancer; in particular, the website provides information on risk factors, screening, and treatment for ovarian cancer (CDC, 2015b).

The CDC created and implemented the Inside Knowledge[2] media campaign to raise awareness among women and health care providers about gynecologic cancers, including cervical, ovarian, uterine, vaginal, and vulvar cancers. The campaign provides information about reliable and proven methods of prevention and early detection (e.g., Pap smears, HPV vaccination) and draws attention to symptoms and changes that could signal gynecologic cancers. By the end of 2014, the campaign had created and distributed media advertisements in digital form, used the Inside Knowledge website to deliver messages, and used print media to reach a large audience of women and their health care providers (CDC, 2015a). Between 2010 and 2014, ads produced for the Inside Knowledge campaign were seen or heard around 3.5 million times, worth a total of $136 million in donated ad value (CDC, 2015b). The CDC also investigates methods to disseminate information. For instance, the CDC found that YouTube can disseminate evidence-based information cheaply and effectively (Cooper et al., 2015).

What Is Ready for Immediate Dissemination?

Through its review of the evidence, the committee identified the following key messages and interventions ready for immediate dissemination

[2]For more information, see http://www.cdc.gov/cancer/knowledge (accessed September 1, 2015).

to help improve the lives of women diagnosed with or at risk for ovarian cancer (see Table 7-1):

- Ovarian cancer is not one disease.
- Current methods for early detection of ovarian cancer in the general or high-risk population do not have substantial impacts on mortality.
- Proven preventive strategies exist, and the risks and benefits need to be discussed between women who are at high risk and their health care providers.
- All women with invasive ovarian cancer should receive germline genetic testing; genetic counseling and testing are also recommended for the first-degree relatives of women with a hereditary cancer syndrome or germline mutation (i.e., cascade testing).
- Uniform implementation of the standard of care and the inclusion of supportive care across the survivorship trajectory can improve outcomes for all women with ovarian cancer.

Table 7-1 shows which messages are appropriate for different stakeholder groups and provides suggested actions for each group. Not all of these messages are appropriate for every stakeholder group. Furthermore, not all of the recommendations in this report are considered ready for D&I; some of them are rather meant to stimulate further research and direct research funding.

D&I Strategies for Specific Stakeholders in Ovarian Cancer

Specific elements of the messages in Table 7-1 can be disseminated to stakeholders right now to help reduce morbidity and mortality from ovarian cancer. The following sections provide a more detailed approach to each of the key audiences to which this report is directed. The committee describes which messages are appropriate for each of the key stakeholder groups and suggests strategies for the D&I for and by these groups.

Patients

The general public can begin to see ovarian cancer as many types of cancer, each with different risk factors and treatment patterns. Women can become more aware of the factors that may increase or decrease the risk for ovarian cancer (e.g., use of oral contraceptives) and consider whether to adopt these choices and lifestyle behaviors. Genetic counseling and testing in families with a history of ovarian, breast, or colon cancer can be a focus of discussions with providers and within families. Discussing genetic coun-

TABLE 7-1
Areas Ready for Dissemination by Each Stakeholder Group

Key Messages	Patients	Families	Health Care Providers	Oncologists	Industry and Payers	Media and Advocacy
"Not one disease" (Rec. 1 & 2)	Many types of ovarian cancers		Subtypes of ovarian cancers	Treatment tailored to subtype		
Genetic testing (Rec. 3 & 7a)	Ask your provider about testing	Request testing for first-degree relatives	Refer patients to testing per guidelines	Use testing results to treat and to discuss with patients	Support testing per guidelines	Testing is relevant for all patients and some families
Risk factors and prevention (Rec. 4 & 5)	Talk to family and provider about risks and prevention	Share family history with providers; consider oral contraceptives				
No effective approach for early detection (Rec. 6)	Need to avoid unproven and potentially invasive screening procedures	Not recommended unless high risk	Do not offer early detection procedures of unproven value		Partner with researchers to develop effective early-detection strategies	Do not advocate messages about early detection without evidence of value
Standard of care (Rec. 7a & 7b)	Consider treatment at high-volume facility			Consider high-volume facility for surgery	Cover some treatment at high-volume facility	Recommend innovative treatment models
Long-term treatment (Rec. 9)	Treatment patterns differ from other cancers		Treatment is long, chronic, and debilitating	Treatment is long, chronic, and debilitating		
Supportive care (Rec. 9)	Require support for broad range of care	Request support for broad range of care	Recommend palliative care	Discuss end-of-life care early in treatment		

seling and testing with all relevant parties might help increase the uptake of testing in high-risk populations.

General media coverage is one method of increasing knowledge in the general public, although this approach may not reach all families at high risk. More effort needs to be made to provide information to women when they are diagnosed and throughout their treatment and care. For example, several interventions and websites have been developed for use with cancer patients and families to improve information exchange and family communication, and these need to be supported in all clinical settings (Lowery et al., 2014).

Women with ovarian cancer may be unable to obtain care from specialty providers or at high-volume centers because they do not live near one of these centers or do not have direct access to such specialists. Providing women with the right questions to ask their providers could be part of the solution. These questions could generate discussion and could be the impetus for more comprehensive care for women with ovarian cancer during and after treatment.

Families

Families in which there are one or more cases of ovarian cancer need to understand the issues surrounding genetic counseling and testing and to consider methods of obtaining such testing. For first-degree relatives of women with ovarian cancer, such testing can provide either an alert of increased risk or reassurance of lower risk. Genetic counseling and testing are available through major medical centers or through direct-to-consumer companies and other sources; families are advised to consult with cancer genetics specialists before undergoing testing. Using general media alerts for these purposes might not be the most efficient method of moving information out to families. The time of diagnosis is a teachable moment for a woman to contact her family and discuss medical information, genetic counseling and testing, and risk reduction options, if appropriate.

For families of women in active treatment for ovarian cancer, understanding and planning for the long-term nature and commitment of such treatment is critical to improving the health of everyone involved with care. Families need to know that the patterns of care are inconsistent and that the treatments will likely continue over months or years. Women, their families, and their caregivers need to be aware of and knowledgeable about the physical and psychosocial sequelae of treatment. Requesting early supportive care for women might be one way that family members can ease the burden on themselves and their diagnosed relative.

Health Care Providers

Primary care providers are often in a position of evaluating the vague, nonspecific symptoms that accompany the first presentation of a woman with ovarian cancer. They are also frequently the provider responsible for the broad, long-term health needs of survivors and their families. Primary care providers, therefore, need to be alert to the common symptoms of ovarian cancer. They also need to be able to access family histories in order to help identify high-risk women and to know when they may need genetic counseling and testing or referral to a gynecologic oncology specialist. Advance care planning is meant to inform primary care providers about care preferences, but these plans are often inadequate and are not yet in full use. Requiring advance care planning at all accredited hospital and clinical facilities is one possible strategy, but the quality and content of such plans varies considerably, as does their ability to inform providers about the need for specific care over time.

Primary care providers are often the first to communicate with women about potential ovarian cancer symptoms and need to resist using unproven early-detection procedures. As more women learn about the possible symptoms of ovarian cancer, they may request screening. Primary care providers may be required to discuss why early detection is not an option with patients and explain that there is currently no endorsed method of ovarian cancer screening in the general population. Finally, primary care providers need to be up to date with the current understanding that ovarian cancer is actually a constellation of multiple diseases with different origins, pathogenesis, and prognoses.

Some of these actions require behavior change in health care providers. Convincing providers to change their medical practices is most successful when incentives are aligned with goals, when people or organizations that providers respect are used to deliver messages, and when providers are given feedback and guidance concerning how what they do with patients affects their performance and their practice quality (Damschroder et al., 2009). Changing provider behavior is often difficult, and relevant research is needed on how to raise awareness of ovarian cancer among primary care providers.

Oncology Providers

The category of oncology providers includes multiple types of providers: oncologists, pathologists, nursing and social workers, and others. Each of these specialties could benefit from disseminated information about ovarian cancer, such as learning about the existence of multiple subtypes and the need for long-term treatment and care. Surgery for ovarian cancer

is now performed in institutions with relatively low rates of ovarian cancer diagnosis and without the surgeons consulting with more highly experienced colleagues. This model of care is suboptimal. New models oriented toward obtaining high-quality surgical care at centralized medical centers (or medical centers working closely in consultation with experts) while maintaining long-term chemotherapy nearer to home need to be developed and supported by oncology providers and payers. If providers would consult with more experienced colleagues, it could improve the quality of care, so this is an option that also needs to be evaluated (Monnier et al., 2003).

As genetic testing becomes more complex and more widepsread in clinical practice, models of care need to be put into place that include clinical geneticists and genetic counselors who can inform patients and families about genetic risk. Genetics experts are often concentrated in high-volume centers, so eHealth models of care (e.g., telephone counseling), which can offer an equivalent method of delivering risk information and results that increases access and which are covered by a growing number of payors, may be an acceptable option (Kinney et al., 2014; Schwartz et al., 2014). Using the Internet or teleonocology could make oncologists more capable of helping care for patients in areas not located near high-volume centers (Shalowitz et al., 2015). One challenge will be how to pay for these remotely delivered services. Another challenge will be how to ensure that all providers are receiving consistent messages and adopting evidence-based practices in a comparable fashion.

Industry and Payers

The plethora of new diagnostic options and therapeutic approaches makes members of industry important stakeholders in ovarian cancer research. Companies that market genetic testing often participate directly in research, working with academicians and clinicians to develop clinically meaningful tests and methods of implementation.

Insurance industry representatives need to be aware of new recommendations for evidence-based treatments and technological applications for ovarian cancer. For example, the health insurance industry could take a lead by paying for care that uses innovative delivery models, such as a model that includes surgery at a high-volume center while covering ongoing treatment and survivorship care closer to home. Covering out-of-network surgery (i.e., surgery performed at a distant high-volume center) would be an important contribution to improving the quality of care for women with ovarian cancer.

The pharmaceutical industry plays a large role in the development and marketing of new therapeutics for ovarian cancer. Collaboration is needed among researchers, clinicians, and industry. This collaboration will likely

result in the more rapid translation of new targeted therapies that allow patients to benefit from advances in precision medicine. The development of tailored treatments for the different ovarian carcinoma subtypes will likely improve treatment outcomes for patients, but will require continued collaborative efforts.

Media and Advocacy Groups

Media and advocacy groups rely on scientific knowledge that they do not generate themselves but that drives their activities in different ways. These types of groups need to have access to a constant flow of cutting-edge information, and they need the tools to discriminate between one-time findings and emerging patterns of important practice-changing findings. Better models of bidirectional information flow, such as those being developed through PCORnet, need to be cultivated for these groups in order to better provide them with the latest scientific findings.

FUTURE RESEARCH

Currently, there is virtually no research on the challenges of D&I for ovarian cancers specifically. This is perhaps not surprising because these cancers are relatively uncommon and because there are significant gaps in the research about their etiology, risk factors, prevention, treatment, and care. This report considers the domain of ovarian cancer research as extending beyond gynecologic oncology to include the roles of primary providers, medical geneticists, epidemiologists, providers of supportive care, industry, advocacy groups, and the media. The committee identified a number of important messages for D&I, including messages about an improved understanding about the heterogeneous nature of ovarian cancers, the origins of these tumors, the value of genetic counseling and testing in high-risk women, and the effectiveness of standards of care.

As discussed previously, the committee identified key messages that are ready for immediate D&I (see Table 7-1). Unlike much of D&I in other areas of health care and prevention, these key messages are not all concerned with interventions of proven effectiveness, but also deal with important knowledge that can, if effectively applied, improve the quality of care and reduce the burden from these cancers. Cancer researchers in the field of translational research (sometimes called T3 or T4 translational research) need to engage in this challenge and explore the use of both traditional methods of communication (e.g., active multimodality educational approaches) and new technologies (e.g., social media) (Khoury et al., 2007). Stakeholders in the areas of ovarian cancer research, clinical care, and advocacy need to support new investigations and coordinate efforts

to develop and implement efficient, effective, and reliable methods for the rapid dissemination and implementation of new evidence-based information and practices. Other areas that require more research in the realm of D&I research include

- Systems for better communication of new clinically significant information and best practices to all kinds of providers;
- Systematic reviews of key elements of care and prevention;
- The movement of new treatments and issues related to care management out to the treating providers;
- The design and evaluation of new models of care for ovarian cancer patients, from initial diagnosis to end-of-life care;
- Information dissemination and practice implementation in low-resource and rural settings;
- Better inclusion of supportive care in comprehensive oncology care; and
- The engagement of the entire family at risk for developing ovarian cancer, both during treatment and in the prevention of future disease.

CONCLUSION AND RECOMMENDATION

This chapter considers "avenues for translation and dissemination of new findings and communication of new information to patients and others" (see Box 1-1 in Chapter 1) by placing the challenge in the content of D&I research. Given the paucity of work in this area, clearly communicated messages are needed on a number of specific topics. Likewise, the committee draws attention to the need for specific D&I research in ovarian cancer to advance the science toward the ultimate goal of reducing both the mortality and morbidity of this disease.

The committee concludes that the while the knowledge base on ovarian cancers has advanced, key stakeholder groups (e.g., patients, families, providers, policy makers, advocates, researchers, and the media) are not receiving important messages that could influence patient outcomes. This may contribute to the current variability seen in the delivery of the standard of care that, in turn, affects patient outcomes. Therefore, the committee recommends the following:

RECOMMENDATION 11: Stakeholders in ovarian cancer research, clinical care, and advocacy should coordinate their efforts to develop and implement efficient, effective, and reliable methods for the rapid dissemination and implementation of evidence-based information and

practices to patients, families, health care providers, advocates, and other relevant parties. These efforts should include

- **Researching impediments to adopting current evidence-based practices;**
- **Using multiple existing dissemination modalities (e.g., continuing education and advocacy efforts) to distribute messages strongly supported by the evidence base; and**
- **Evaluating newer pathways of dissemination and implementation (e.g., social media and telemedicine with specialists).**

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Appendix A

Acronyms and Abbreviations

ABOG	American Board of Obstetrics and Gynecology
ABOUT	American BRCA Outcomes and Utilization of Testing [Patient-Powered Research Network]
ACA	Patient Protection and Affordable Care Act
ACMG	American College of Medical Genetics and Genomics
ACOG	American Congress of Obstetricians and Gynecologists
ACS	American College of Surgeons
ACT	adoptive cell therapy
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
BER	base excision repair
BMI	body mass index
BOT	borderline ovarian tumor
BRCA	breast cancer genes 1 and 2
BSO	bilateral salpingo-oophorectomy
BSOR	bilateral salpingectomy with ovarian retention
CA-125	cancer antigen 125
CAM	complementary and alternative medicine
CCC	clear cell carcinoma
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CPTAC	Clinical Proteomic Tumor Analysis Consortium
CT	computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
D&I	dissemination and implementation
DNA	deoxyribonucleic acid
DoD	U.S. Department of Defense
EBI	evidence-based intervention
EC	endometrioid carcinoma
EGFR	epidermal growth factor receptor
EMT	epithelial to mesenchymal transition
FDA	U.S. Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FORCE	Facing Our Risk of Cancer Empowered
FTE	fallopian tube epithelium
GEMM	genetically engineered mouse model
GH	growth hormone
GOG	Gynecologic Oncology Group
HBOC	hereditary breast and ovarian cancer [syndrome]
HE-4	human epididymis protein 4
HGSC	high-grade serous carcinoma
HHS	U.S. Department of Health and Human Services
HPV	human papillomavirus
HR	homologous recombination
IGF-1	insulin-like growth factor 1
IOM	Institute of Medicine
IP	intraperitoneal
IrRC	immune-related response criteria
IV	intravenous
LBA	laboratory biomarker analysis
LGSC	low-grade serous carcinoma
MAPK	mitogen-activated protein kinase
MC	mucinous carcinoma
miR	microRNA
MMS	multimodal screening
MRI	magnetic resonance imaging

NACT	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NHEJ	nonhomologous end joining
NIH	National Institutes of Health
NOCC	National Ovarian Cancer Coalition
NRC	National Research Council
NSGC	National Society of Genetic Counselors
OC	oral contraceptive
OCNA	Ovarian Cancer National Alliance
OCRF	Ovarian Cancer Research Fund
OCRP	Ovarian Cancer Research Program
OCS	Office of Cancer Survivorship
OSE	ovarian surface epithelium
PARP	poly ADP ribose polymerase
PCORI	Patient-Centered Outcomes Research Institute
PCOS	polycystic ovarian syndrome
PDS	primary debulking surgery
PDX	patient-derived xenograft
PFS	progression-free survival
PID	pelvic inflammatory disease
PLCO	prostate, lung, colorectal, and ovarian [cancer screening trial]
PPC	primary palliative care
PRO	patient-reported outcome
QOL	quality of life
RCT	randomized controlled trial
RMI	Risk of Malignancy Index
RNA	ribonucleic acid
ROCA	risk of ovarian cancer algorithm
ROMA	risk of ovarian malignancy algorithm
RRSO	risk-reducing salpingo-oophorectomy
SBT	serous borderline tumor
SEER	surveillance, epidemiology, and end results
SGO	Society of Gynecologic Oncology
SNP	single-nucleotide polymorphism
SPC	specialty palliative care

SPORE	Specialized Program of Research Excellence
STIC	serous tubal intraepithelial carcinoma
TCGA	The Cancer Genome Atlas
TVU	transvaginal ultrasound
UKCTOCS	United Kingdom Collaborative Trial of Ovarian Cancer Screening
USPSTF	U.S. Preventive Services Task Force
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOO	window of opportunity

Appendix B

Glossary

Adjuvant therapy—Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy (NCI, 2015a).

Adnexal mass—A lump in tissue near the uterus, usually in the ovary or fallopian tube. Adnexal masses include ovarian cysts, ectopic (tubal) pregnancies, and benign (not cancer) or malignant (cancer) tumors (NCI, 2015a).

Allele—One of two or more DNA sequences occurring at a particular gene locus. Typically one allele ("normal" DNA sequence) is common, and other alleles (mutations) are rare (NCI, 2015b).

Angiogenesis—Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This process is caused by the release of chemicals by the tumor and by host cells near the tumor (NCI, 2015a).

Benign—Not cancerous. Benign tumors may grow larger but do not spread to other parts of the body. Also called nonmalignant (NCI, 2015a).

Bilateral salpingo-oophporectomy—Surgery to remove both ovaries and both fallopian tubes (NCI, 2015a).

Biomarker—A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule (NCI, 2015a).

BRCA1—A gene on chromosome 17 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a *BRCA1* gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer (NCI, 2015a).

BRCA2—A gene on chromosome 13 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a *BRCA2* gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer (NCI, 2015a).

CA-125—A substance that may be found in high amounts in the blood of patients with certain types of cancer, including ovarian cancer. CA-125 levels may also help monitor how well cancer treatments are working or if cancer has come back. Also called cancer antigen 125 (NCI, 2015a).

Cancer—A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems (NCI, 2015a).

Cancer care continuum—The trajectory from cancer prevention and risk reduction, through screening, diagnosis, treatment, survivorship, and end-of-life care (adapted from NCI, 2011).

Carcinogen—Any substance that causes cancer (NCI, 2015a).

Carcinoma—Cancer that begins in the skin or in tissues that line or cover internal organs (NCI, 2015a).

Chemosensitivity—The susceptibility of tumor cells to the cell-killing effects of anticancer drugs (NCI, 2015a).

Comparative effectiveness research (CER)—The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and the population levels (IOM, 2009).

Copy number variant—Refers to the genetic trait involving the number of copies of a particular gene present in the genome of an individual. Genetic variants, including insertions, deletions, and duplications of segments of DNA, are also collectively referred to as copy number variants. Copy number variants account for a significant proportion of the genetic variation between individuals (NCI, 2015b).

Debulking—Also known as cytoreduction, the surgical removal of as much of a tumor as possible. Debulking may increase the chance that chemotherapy or radiation therapy will kill all the tumor cells. It may also be done to relieve symptoms or help the patient live longer. Also called tumor debulking (NCI, 2015a).

Disease-free survival—In cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works (NCI, 2015a).

Epigenomics—The study of all of the epigenetic changes in a cell. Epigenetic changes are changes in the way genes are switched on and off without changing the actual DNA sequence. They may be caused by age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals. Epigenetic changes can affect a person's risk of disease and may be passed from parents to their children (NCI, 2015a).

False negative—A test result that indicates that a person does not have a specific disease or condition when the person actually does have the disease or condition (NCI, 2015a).

False positive—A test result that indicates that a person has a specific disease or condition when the person actually does not have the disease or condition (NCI, 2015a).

Genetic instability—A high frequency of mutations within the genome of a cellular lineage (Negrini et al., 2010).

Genome-wide association study—A way for scientists to identify inherited genetic variants associated with risk of disease or a particular trait. This method surveys the entire genome for genetic polymorphisms, typically single-nucleotide polymorphisms, that occur more frequently in cases (people with the disease or trait being assessed) than in controls (people without the disease or trait) (NCI, 2015b).

Genomics—The study of the complete genetic material, including genes and their functions, of an organism (NCI, 2015a).

Germline DNA—The DNA in germ cells (egg and sperm cells that join to form an embryo). Germline DNA is the source of DNA for all other cells in the body. Also called constitutional DNA (NCI, 2015a).

Germline mutation—A gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Also called hereditary mutation (NCI, 2015a).

HE-4—A gene amplified in ovarian carcinomas, whereas its expression in normal tissues, including ovary, is low. It is used as a biomarker for ovarian carcinoma (Hellstrom et al., 2003).

Hereditary cancer syndrome—A type of inherited disorder in which there is a higher-than-normal risk of certain types of cancer. Hereditary cancer syndromes are caused by mutations (changes) in certain genes passed from parents to children. In a hereditary cancer syndrome, certain patterns of cancer may be seen within families. These patterns include having several close family members (such as a mother, daughter, and sister) with the same type of cancer, developing cancer at an early age, or having two or more types of cancer develop in the same person (NCI, 2015a).

Heterogeneity—Made up of elements that are not alike (NCI, 2015a).

Histology—The study of tissues and cells under a microscope (NCI, 2015a).

Histopathology—The study of diseased cells and tissues using a microscope (NCI, 2015a).

Histotype—Any of a range of tissue types that arise during the growth of a tumor (NCI, 2015a).

Incidence—The number of new cases of a disease diagnosed over a certain period of time (NCI, 2015a).

Interval debulking surgery—Surgical removal of as much of a tumor as possible during primary chemotherapy with further chemotherapy to follow (adapted from NCI, 2015a).

Intraperitoneal chemotherapy—Treatment in which anticancer drugs are put directly into the abdominal cavity through a thin tube (NCI, 2015a).

Malignancy—Also called cancer (NCI, 2015a).

Malignant—Cancerous. Malignant cells can invade and destroy nearby tissue and spread to other parts of the body (NCI, 2015a).

Metabolomics—The study of substances called metabolites in cells and tissues. Metabolites are small molecules that are made when the body breaks down food, drugs, chemicals, or its own tissue. They can be measured in blood, urine, and other body fluids. Disease and environmental factors, such as diet, drugs, and chemicals, can affect how metabolites are made and used in the body (NCI, 2015a).

Metastasis—The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases (NCI, 2015a).

Molecular diagnosis—The process of identifying a disease by studying molecules such as proteins, DNA, and RNA in a tissue or fluid (NCI, 2015a).

Molecular marker—See definition for biomarker.

Molecular pathway—A series of actions among molecules in a cell that leads to a certain end point or cell function (NCI, 2015a).

Molecular risk assessment—A procedure in which biomarkers (for example, biological molecules or changes in tumor cell DNA) are used to estimate a person's risk for developing cancer. Specific biomarkers may be linked to particular types of cancer (NCI, 2015a).

Molecular test—In medicine, a laboratory test that checks for certain genes, proteins, or other molecules in a sample of tissue, blood, or other body fluid. Molecular tests also check for certain changes in a gene or chromosome that may cause or affect the chance of developing a specific disease or disorder, such as cancer. A molecular test may be done with other procedures, such as biopsies, to help diagnose some types of cancer. It may also be used to help plan treatment, find out how well treatment is working, or make a prognosis (NCI, 2015a).

Molecularly targeted therapy—In cancer treatment, substances that kill cancer cells by targeting key molecules involved in cancer growth (NCI, 2015a).

Morbidity—Refers to having a disease or a symptom of disease, or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment (NCI, 2015a).

Mortality—Refers to the state of being mortal (destined to die). In medicine, a term also used for death rate, or the number of deaths in a certain group of people in a certain period of time. Mortality may be reported for people who have a certain disease, live in one area of the country, or who are of a certain gender, age, or ethnic group (NCI, 2015a).

Neoadjuvant chemotherapy (NACT)—Neoadjuvant therapy is a treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy (NCI, 2015a).

Next-generation sequencing (NGS)—A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome. This technique utilizes DNA-sequencing technologies that are capable of processing multiple DNA sequences in parallel. Also called massively parallel sequencing and NGS (NCI, 2015b).

Omics—Scientific disciplines comprising study of related sets of biological molecules. Examples of omics disciplines include genomics, transcriptomics, proteomics, metabolomics, and epigenomics (IOM, 2012).

Oophorectomy—Surgery to remove one or both ovaries (NCI, 2015a).

Overall survival—The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works (NCI, 2015a).

PARP inhibitor—A substance that blocks an enzyme in cells called PARP. PARP helps repair DNA when it becomes damaged. DNA damage may be caused by many things, including exposure to ultraviolet light, radiation, certain anticancer drugs, or other substances in the environment. In cancer treatment, blocking PARP may help keep cancer cells from repairing their

damaged DNA, causing them to die. PARP inhibitors are a type of targeted therapy. Also called poly (ADP-ribose) polymerase inhibitor (NCI, 2015a).

Patient-reported outcome (PRO)—A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response. (FDA, 2009).

Peritoneum—The tissue that lines the abdominal wall and covers most of the organs in the abdomen (NCI, 2015a).

Polymorphism—A common change in the genetic code in DNA. Polymorphisms can have a harmful effect, a good effect, or no effect. Some polymorphisms have been shown to increase the risk of certain types of cancer (NCI, 2015a).

Prevalence—The number of existing cases of a disease at one point in time (NCI, 2008).

Progression-free survival—The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works (NCI, 2015a).

Proteomics—The study of the structure and function of proteins, including the way they work and interact with each other inside cells (NCI, 2015a).

Psychosocial—In medicine, describes the psychological (emotional) and social parts of a disease and its treatment. Some of the psychosocial parts of cancer are its effects on patients' feelings, moods, beliefs, the way they cope, and relationships with family, friends, and co-workers (NCI, 2015a).

Recurrence—Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body. Also called recurrent or relapsed cancer (NCI, 2015a).

Relapse—The return of a disease or the signs and symptoms of a disease after a period of improvement (NCI, 2015a).

Residual disease—Cancer cells that remain after attempts to remove the cancer have been made (NCI, 2015a).

Salpingectomy—Surgical removal of the fallopian tubes (NCI, 2015a).

Salpingo-oophorectomy—Surgical removal of the fallopian tubes and ovaries (NCI, 2015a).

Sensitivity—When referring to a medical test, sensitivity refers to how well a test can detect a specific disease or condition in people who actually have the disease or condition. No test has 100 percent sensitivity because some people who have the disease or condition will not be identified by the test (see false negative) (NCI, 2015a).

Single-nucleotide polymorphism (SNP)—The most common type of change in DNA (molecules inside cells that carry genetic information). SNPs occur when a single nucleotide (building block of DNA) is replaced with another. These changes may cause disease, and may affect how a person reacts to bacteria, viruses, drugs, and other substances (NCI, 2015a).

Specificity—When referring to a medical test, specificity refers to the percentage of people who test negative for a specific disease among a group of people who do not have the disease. No test is 100 percent specific because some people who do not have the disease will test positive for it (see false positive) (NCI, 2015a).

Staging—Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment (NCI, 2015a).

Survivor—One who remains alive and continues to function during and after overcoming a serious hardship or life-threatening disease. In cancer, a person is considered to be a survivor from the time of diagnosis until the end of life (NCI, 2015a).

Survivorship—In cancer, survivorship focuses on the health and life of a person with cancer post-treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancers, and quality of life. Family members, friends, and caregivers are also considered part of the survivorship experience (NCI, 2015a).

Telomere—The ends of a chromosome. Each time a cell divides, the telomeres lose a small amount of DNA and become shorter. Over time, the chromosomes become damaged and the cells die. In cancer cells the telomeres do not get shorter, and may become longer, as the cells divide (NCI, 2015a).

TP53—A tumor suppressor gene that normally inhibits the growth of tumors. This gene is altered in many types of cancer (NCI, 2015a).

Tumor—An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign or malignant (NCI, 2015a).

Tumor burden—Refers to the number of cancer cells, the size of a tumor, or the amount of cancer in the body. Also called tumor load (NCI, 2015a).

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Appendix C

Open and Active Clinical Trials on Epithelial Ovarian Cancer[1]

This appendix includes a listing of the clinical trials in epithelial ovarian cancer that are open and recruiting, open and not yet recruiting (denoted by an asterisk), or active but closed to recruiting as of the writing of this report. The data in this table were generated by a search performed on www.ClinicalTrials.gov on December 4, 2015, using the subtopic of "epithelial ovarian cancer." Studies with an "unknown" status have been excluded. This search resulted in 204 interventional studies and 31 observational studies. The studies are presented in the following table by study phase and by study type (interventional versus observational). The table lists the types of interventions used in each study, but does not include placebos (where used), nor the different types of administration of the same intervention (e.g., different dosage amounts of the same drug).

The purpose of this appendix is to give a broader sense of the types of studies that are under way as well as to give a sense of the priority areas of focus. This appendix is not intended to serve as an exhaustive list of all studies currently under way in ovarian cancer. The committee also acknowledges that many of these studies are not limited to ovarian cancers. Furthermore, the committee acknowledges that by limiting the list to studies that specifically target epithelial ovarian cancers, the many more studies being performed on ovarian cancers in general are excluded. A similar search done under the subtopic of ovarian cancer in general revealed 385 open studies and 223 studies that are closed and active but not recruiting. These numbers likely include the studies listed in this appendix.

[1] Open trials listed on www.ClinicalTrials.gov as of December 4, 2015.

NCT Number	Title	Drug Intervention
Phase I Interventional Studies		
NCT01536054	Sirolimus and Vaccine Therapy in Treating Patients With Stage II–IV Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cavity Cancer	Sirolimus
NCT01155258	Temsirolimus and Vinorelbine Ditartrate in Treating Patients With Unresectable or Metastatic Solid Tumors	Temsirolimus; vinorelbine ditartrate
NCT00357448	Denileukin Diftitox Used in Treating Patients With Advanced Refractory Ovarian Cancer, Primary Peritoneal Carcinoma, or Epithelial Fallopian Tube Cancer	N/A
NCT01074411	Intraperitoneal Bortezomib and Carboplatin in Treating Patients With Persistent or Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Bortezomib; carboplatin
NCT01322802	Vaccine Therapy in Treating Patients With Stage III–IV or Recurrent Ovarian Cancer	N/A
NCT00436254	Vaccine Therapy With Sargramostim (GM-CSF) in Treating Patients With HER-2 Positive Stage III–IV Breast Cancer or Ovarian Cancer	N/A
NCT02046421	Carboplatin, Gemcitabine Hydrochloride, and Mifepristone in Treating Patients With Advanced Breast Cancer or Recurrent or Persistent Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cancer	Mifepristone; carboplatin; gemcitabine hydrochloride
NCT00602277	Viral Therapy in Treating Patients With Ovarian Epithelial Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer That Did Not Respond to Platinum Chemotherapy	N/A
NCT01715168	A Crossover Bioequivalence Study of Intravenously Administered ATI-0918 and DOXIL/CAELYX in Patients With Ovarian Cancer	DOXIL/CAELYX; ATI-0918

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine; sargramostim	Laboratory biomarker analysis (LBA)	7	Roswell Park Cancer Institute; National Cancer Institute (NCI); Sanofi Pasteur, a Sanofi Company
N/A	N/A	19	University of Southern California; Wyeth (now a wholly owned subsidiary of Pfizer)
Denileukin diftitox	LBA; intraperitoneal (IP) administration; enzyme-linked immunosorbent assay; flow cytometry	11	University of Washington; NCI
N/A	LBA; pharmacological study	36	NCI
pUMVC3-hIGFBP-2 multi-epitope plasmid DNA vaccine	LBA	22	University of Washington; NCI
pNGVL3-hICD vaccine; sargramostim	Flow cytometry; immunologic technique; immunoenzyme technique; protein expression analysis; biopsy	66	University of Washington; NCI
N/A	LBA; pharmacological study	22	University of Chicago; NCI
Wild-type reovirus	LBA	14	NCI
N/A	N/A	40	Azaya Therapeutics, Inc.

NCT Number	Title	Drug Intervention
NCT01940172	Study of Birinapant in Combination With Conatumumab in Subjects With Relapsed Ovarian Cancer	Birinapant; conatumumab
NCT01459380	Veliparib, Pegylated Liposomal Doxorubicin Hydrochloride, Carboplatin, and Bevacizumab in Treating Patients With Recurrent Ovarian Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer	Carboplatin; pegylated liposomal doxorubicin hydrochloride; veliparib
NCT02270372	Study of ONT-10 and Varlilumab to Treat Advanced Ovarian or Breast Cancer	N/A
NCT00562640	Autologous T Cells With or Without Cyclophosphamide and Fludarabine in Treating Patients With Recurrent or Persistent Advanced Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer (Fludarabine Treatment Closed as of 12/01/2009)	Cyclophosphamide
NCT00408590	Recombinant Measles Virus Vaccine Therapy and Oncolytic Virus Therapy in Treating Patients With Progressive, Recurrent, or Refractory Ovarian Epithelial Cancer, or Primary Peritoneal Cancer	N/A
NCT02159716	CART-meso in Mesothelin Expressing Cancers	N/A
NCT01649336	A Study of MEK162 and Paclitaxel in Patients With Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer	MEK162, MEK inhibitor (oral); paclitaxel, mitotic inhibitor (intravenous)

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	40	TetraLogic Pharmaceuticals
Bevacizumab	LBA	48	NCI
ONT-10, varlilumab combination	N/A	42	Oncothyreon, Inc.; Celldex Therapeutics
Filgrastim; therapeutic autologous lymphocytes	LBA	21	Memorial Sloan Kettering Cancer Center; NCI
Carcinoembryonic antigen-expressing measles virus; oncolytic measles virus encoding thyroidal sodium iodide symporter reaction	LBA; reverse transcriptase-polymerase chain	46	Mayo Clinic; NCI
CART-meso	N/A	21	Abramson Cancer Center of the University of Pennsylvania
N/A	N/A	36	Array BioPharma

NCT Number	Title	Drug Intervention
NCT01121640	A Trial Using Novel Markers to Predict Malignancy in Elevated-Risk Women	N/A
NCT01286987	Study of BMN 673, a PARP Inhibitor, in Patients With Advanced or Recurrent Solid Tumors	BMN 673
NCT01606241	Vaccine Therapy and Cyclophosphamide in Treating Patients With Stage II–III Breast or Stage II–IV Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Cyclophosphamide
NCT01522820	Vaccine Therapy With or Without Sirolimus in Treating Patients With NY-ESO-1 Expressing Solid Tumors	Sirolimus
NCT01264432	Veliparib and Radiation Therapy in Treating Patients With Advanced Solid Malignancies With Peritoneal Carcinomatosis, Epithelial Ovarian, Fallopian, or Primary Peritoneal Cancer	Veliparib
NCT00892736	Veliparib in Treating Patients With Malignant Solid Tumors That Did Not Respond to Previous Therapy	Veliparib
NCT00410553	Eribulin Mesylate and Gemcitabine Hydrochloride in Treating Patients With Metastatic Solid Tumors or Solid Tumors That Cannot be Removed by Surgery	Eribulin mesylate; gemcitabine hydrochloride
NCT01220154	Study of Intraperitoneal Carboplatin With IV Paclitaxel and Bevacizumab in Untreated Ovarian Cancer	Bevacizumab; paclitaxel; carboplatin

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	CA-125 assay on Abbott Architect i1000SR platform; HE4 assay on Architect i1000SR platform; transvaginal ultrasound	1,208	Fred Hutchinson Cancer Research Center; The Marsha Rivkin Center for Ovarian Cancer Research; Canary Foundation; Swedish Medical Center; Beckman Research Institute; Cedars-Sinai Medical Center; Stanford University; Fox Chase Cancer Center
N/A	N/A	113	BioMarin Pharmaceutical
Multi-epitope folate receptor alpha peptide vaccine	LBA	24	Mayo Clinic; NCI
DEC-205/NY-ESO-1 fusion protein CDX-1401	LBA; pharmacological study	30	Roswell Park Cancer Institute; NCI
N/A	LBA; quality-of-life (QOL) assessment; radiation therapy	40	NCI
N/A	LBA; pharmacological study	120	NCI
N/A	N/A	45	NCI
N/A	N/A	9	David O'Malley; Genentech, Inc.; Ohio State University Comprehensive Cancer Center

NCT Number	Title	Drug Intervention
NCT01314105	BIBF 1120 + Carboplatin/Pegylated Liposomal Doxorubicin (PLD) in Patients With Advanced Ovarian Cancer, Fallopian Tube Carcinoma, or Primary Peritoneal Cancer	BIBF 1120 + PLD 30 mg/m2 + CBDCA AUC5 mg/mL*min
NCT00825201	Intraperitoneal Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Advanced Cancer of the Peritoneal Cavity	Paclitaxel albumin-stabilized nanoparticle formulation
NCT00652691	Topotecan, High-Dose Cyclophosphamide, Carboplatin, and an Autologous Peripheral Blood Cell Transplant in Treating Patients With Recurrent Ovarian Cancer or Primary Peritoneal Cancer	Carboplatin; cyclophosphamide; topotecan hydrochloride
NCT01445418	AZD2281 Plus Carboplatin to Treat Breast and Ovarian Cancer	AZ2281 + carboplatin
NCT02083536*	LDFWART With Docetaxel in Patients With Platinum-Resistant Recurrent Ovarian Carcinoma	Docetaxel
NCT02275039*	p53MVA Vaccine and Gemcitabine Hydrochloride in Treating Patients With Recurrent Ovarian Epithelial Cancer	Gemcitabine hydrochloride
NCT01489371*	EGEN-001 and Pegylated Liposomal Doxorubicin Hydrochloride in Treating Patients With Recurrent or Persistent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Pegylated liposomal doxorubicin hydrochloride
NCT01249443*	Vorinostat in Combination With Paclitaxel and Carboplatin in Treating Patients With Metastatic or Recurrent Solid Tumors and HIV Infection	Vorinostat; carboplatin; paclitaxel
NCT02606305*	Study of IMGN853 in Comb. With Bevacizumab, Carboplatin, or PLD in Adults With FRa + Adv. EOC, Primary Peritoneal, Fallopian Tube, or Endometrial Cancer	IMGN853; bevacizumab; carboplatin; doxorubicin
NCT02260544*	Bioequivalence Study of Doxorubicin Hydrochloride Liposome Injection	Doxorubicin hydrochloride liposome injection
NCT02014337*	Mifepristone and Eribulin in Patients With Metastatic Triple Negative Breast Cancer or Other Specified Solid Tumors	Mifepristone and eribulin in combination

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	19	Boehringer Ingelheim
N/A	Liquid chromatography; mass spectrometry; pharmacological study; LBA	29	City of Hope Medical Center; NCI; National Comprehensive Cancer Network
Filgrastim	Autologous hematopoietic stem cell transplantation; peripheral blood stem cell transplantation	48	Mayo Clinic; NCI
N/A	N/A	103	NCI; National Institutes of Health Clinical Center (CC)
N/A	Low-dose fractionated whole abdominal radiation therapy	12	University of Miami
Modified vaccinia virus ankara vaccine expressing p53	LBA	9	City of Hope Medical Center; NCI
EGEN-001	LBA	18	Gynecologic Oncology Group; NCI
N/A	Diagnostic LBA; pharmacological study	26	AIDS Malignancy Consortium; NCI; The EMMES Corporation
N/A	N/A	145	ImmunoGen, Inc.
N/A	N/A	48	Dr. Reddy's Laboratories Limited
N/A	N/A	40	Corcept Therapeutics

NCT Number	Title	Drug Intervention
NCT02083536*	LDFWART With Docetaxel in Patients With Platinum-Resistant Recurrent Ovarian Carcinoma	Docetaxel
NCT02275039*	p53MVA Vaccine and Gemcitabine Hydrochloride in Treating Patients With Recurrent Ovarian Epithelial Cancer	Gemcitabine hydrochloride
NCT01489371*	EGEN-001 and Pegylated Liposomal Doxorubicin Hydrochloride in Treating Patients With Recurrent or Persistent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Pegylated liposomal doxorubicin hydrochloride
NCT01249443*	Vorinostat in Combination With Paclitaxel and Carboplatin in Treating Patients With Metastatic or Recurrent Solid Tumors and HIV Infection	Vorinostat; carboplatin; paclitaxel
NCT02606305*	Study of IMGN853 in Comb. With Bevacizumab, Carboplatin or PLD in Adults With FRa + Adv. EOC, Primary Peritoneal, Fallopian Tube, or Endometrial Cancer	IMGN853; bevacizumab; carboplatin; doxorubicin
NCT02260544*	Bioequivalence Study of Doxorubicin Hydrochloride Liposome Injection	Doxorubicin hydrochloride liposome injection
NCT02014337*	Mifepristone and Eribulin in Patients With Metastatic Triple Negative Breast Cancer or Other Specified Solid Tumors	Mifepristone and eribulin in combination
NCT02520115*	Folate Receptor in Diagnosing Ovarian Cancer Using Serum Samples from Patients With Newly Diagnosed Pelvic Mass or Previously Diagnosed Ovarian Cancer	Dexamethasone; valproic acid
NCT01281514*	Carboplatin, Pegylated Liposomal Doxorubicin Hydrochloride, and Everolimus in Treating Patients With Relapsed Ovarian Epithelial, Fallopian Tube, or Peritoneal Cavity Cancer	Everolimus; carboplatin; pegylated liposomal doxorubicin hydrochloride
NCT02480374*	Study of Safety & Biological Activity of IP GEN-1 With Neoadjuvant Chemo in Ovarian Cancer	N/A
NCT02324439*	Flaxseed as Maintenance Therapy for Ovarian Cancer Patients in Remission	N/A
NCT02312661*	Study of Metformin With Carboplatin/ Paclitaxel Chemotherapy in Patients With Advanced Ovarian Cancer	Metformin; paclitaxel; carboplatin

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Low-dose fractionated whole abdominal radiation therapy	12	University of Miami
Modified vaccinia virus ankara vaccine expressing p53	LBA	9	City of Hope Medical Center; NCI
EGEN-001	LBA	18	Gynecologic Oncology Group; NCI
N/A	Diagnostic LBA; pharmacological study	26	AIDS Malignancy Consortium; NCI; The EMMES Corporation
N/A	N/A	145	ImmunoGen, Inc.
N/A	N/A	48	Dr. Reddy's Laboratories Limited
N/A	N/A	40	Corcept Therapeutics
N/A	LBA	180	Barbara Ann Karmanos Cancer Institute; NCI
N/A		24	Fox Chase Cancer Center
GEN-1	N/A	15	Celsion
N/A	Omega Nutrition cold-milled flaxseeds	90	Southern Illinois University
N/A	N/A	20	University Medical Center Groningen

NCT Number	Title	Drug Intervention
NCT02534922*	Study of Prolanta™ in Recurrent or Persistent Epithelial Ovarian Cancer	N/A
NCT02470559*	Activated T-cell Therapy, Low-Dose Aldesleukin, and Sargramostim in Treating Patients With Ovarian, Fallopian Tube, or Primary Peritoneal Cancer That Is Stage III–IV, Refractory, or Recurrent	N/A
NCT02432963*	Vaccine Therapy and Pembrolizumab in Treating Patients With Solid Tumors That Have Failed Prior Therapy	N/A
NCT02298959*	Pembrolizumab and Ziv-aflibercept in Treating Patients With Advanced Solid Tumors	N/A
NCT02142803*	TORC1/2 Inhibitor MLN0128 and Bevacizumab in Treating Patients With Recurrent Glioblastoma or Advanced Solid Tumors	TORC1/2 inhibitor INK128
NCT01145430*	Veliparib and Pegylated Liposomal Doxorubicin Hydrochloride in Treating Patients With Recurrent Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer or Metastatic Breast Cancer	Pegylated liposomal doxorubicin hydrochloride; veliparib
NCT02344095*	A Trial of Weekly Paclitaxel With Oncothermia and Weekly Cisplatin With Oncothermia in Patients With Recurrent or Persistent Ovarian Cancer	Weekly paclitaxel; weekly cisplatin
NCT00989651*	Carboplatin, Paclitaxel, Bevacizumab, and Veliparib in Treating Patients With Newly Diagnosed Stage II–IV Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cancer	Carboplatin; cisplatin; paclitaxel; veliparib
NCT02199171*	Heated Carboplatin in Treating Patients With Stage II–IV Ovarian, Fallopian Tube, or Peritoneal Cancer	Carboplatin
NCT01665183*	Ph 1 Trial of ADI-PEG 20 Plus Cisplatin in Patients With Metastatic Melanoma	ADI-PEG 20
NCT02000778*	EC17 for Intraoperative Imaging in Occult Ovarian Cancer	EC17

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
Prolanta, a human prolactin receptor antagonist	N/A	18	Oncolix, Inc.
Aldesleukin; HER2Bi-armed activated T cells; sargramostim	LBA	20	Barbara Ann Karmanos Cancer Institute; NCI
Modified vaccinia virus ankara vaccine expressing p53; pembrolizumab	LBA	12	City of Hope Medical Center; NCI
Pembrolizumab; ziv-aflibercept	LBA	36	NCI
Bevacizumab	LBA; pharmacological study	60	NCI
N/A	LBA; pharmacological study	58	NCI
N/A	Oncothermia	12	Seoul National University Hospital
Bevacizumab	LBA	474	NCI
N/A	N/A	30	University of California, Irvine
N/A	N/A	89	Polaris Group
N/A	N/A	10	University of Pennsylvania

NCT Number	Title	Drug Intervention
NCT02530047*	Mesenchymal Stem Cells (MSC) for Ovarian Cancer	N/A
NCT02303912*	Safety and Efficacy Study of Nuc-1031 and Carboplatin Combination to Treat Recurrent Ovarian Cancer	Nuc-1031; carboplatin
NCT02534922*	Study of Prolanta™ in Recurrent or Persistent Epithelial Ovarian Cancer	N/A
NCT02627430*	Talazoparib and HSP90 Inhibitor AT13387 in Treating Patients With Metastatic Advanced Solid Tumor or Recurrent Ovarian, Fallopian Tube, Primary Peritoneal, or Triple Negative Breast Cancer	HSP90 inhibitor AT13387; talazoparib
NCT02530047*	Mesenchymal Stem Cells (MSC) for Ovarian Cancer	N/A
Phase I/II Interventional Studies		
NCT00553683	Cyclophosphamide, Radiation Therapy, and Poly ICLC in Treating Patients With Unresectable, Recurrent, Primary, or Metastatic Liver Cancer	Cyclophosphamide; poly ICLC
NCT01472783	Veliparib Monotherapy for Relapsed Ovarian Cancer With BRCA Mutation	Veliparib
NCT01091428	MLN8237 in Patients With Ovarian, Fallopian Tube or Peritoneal Cancer Preceded by Phase 1 Study of MLN8237 Plus Paclitaxel Treatment of Ovary or Breast Cancer	MLN8237 + paclitaxel
NCT01238770	Phase I/II Study of Pazopanib and Cyclophosphamide in Patients With Platinum-Resistant Recurrent Ovarian Cancer	Pazopanib
NCT00317772	Topotecan and Gefitinib (Iressa) for Ovarian, Peritoneal, or Fallopian Tube Cancer	Topotecan; gefitinib
NCT02244502*	Safety, Feasibility, and Effect of TTFields Concomitant With Weekly Paclitaxel in Recurrent Ovarian Carcinoma	Paclitaxel
NCT01709487*	Feasibility Study of HIPEC for Patients With Stage III or Only Pleural Stage IV Ovarian Carcinoma in First-Line Therapy	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	MSC-INFβ; questionnaires	21	MD Anderson Cancer Center
N/A	N/A	36	Imperial College Healthcare NHS Trust
Prolanta, a human prolactin receptor antagonist	N/A	18	Oncolix, Inc.
N/A	LBA; pharmacological study	40	NCI
MSC-INFβ	Questionnaires	21	MD Anderson Cancer Center
N/A	Hepatic artery embolization; 3-dimensional conformal radiation therapy	50	Rutgers, The State University of New Jersey
N/A	N/A	49	Vejle Hospital; Abbott
N/A	N/A	172	Millennium Pharmaceuticals, Inc.
N/A	N/A	57	Priv.-Doz. Dr. med. Joachim Rom; University Hospital Heidelberg
N/A	N/A	52	MD Anderson Cancer Center; AstraZeneca; GlaxoSmithKline
N/A	NovoTTF-100L(O) (device)	30	NovoCure, Ltd.
N/A	Hyperthermic intra-peritoneal chemotherapy (HIPEC)	24	Jules Bordet Institute

NCT Number	Title	Drug Intervention
NCT01631552*	Phase I/II Study of IMMU-132 in Patients With Epithelial Cancers	IMMU-132
NCT01962948*	Paclitaxel and Ganetespib in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Paclitaxel; ganetespib
NCT02068794*	MV-NIS Infected Mesenchymal Stem Cells in Treating Patients With Recurrent Ovarian Cancer	N/A
NCT01402271*	Pazopanib Hydrochloride, Paclitaxel, and Carboplatin in Treating Patients With Refractory or Resistant Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Peritoneal Cancer	Carboplatin; paclitaxel; pazopanib hydrochloride
NCT02584478*	A Phase 1/2a Evaluation of the Safety and Efficacy of Adding AL3818 to Standard Platinum-Based Chemotherapy	AL3818; carboplatin; paclitaxel
NCT02335918*	A Dose Escalation and Cohort Expansion Study of Anti-CD27 (Varlilumab) and Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors	Combination of varlilumab and nivolumab
NCT02166905*	DEC-205/NY-ESO-1 Fusion Protein CDX-1401, Poly ICLC, and IDO1 Inhibitor INCB024360 in Treating Patients With Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Remission	Poly ICLC; IDO1 inhibitor INCB024360
NCT02012192*	GANNET53: Ganetespib in Metastatic, p53-Mutant, Platinum-Resistant Ovarian Cancer	Ganetespib; paclitaxel
NCT01663857*	A Study of LY2228820 for Recurrent Ovarian Cancer	LY2228820; carboplatin; gemcitabine
NCT01116648*	Cediranib Maleate and Olaparib in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Peritoneal Cancer or Recurrent Triple-Negative Breast Cancer	Cediranib maleate; olaparib
NCT02028117*	Phase I/II Study of Enadenotucirev Intraperitoneally in Ovarian Cancer Patients	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	250	Immunomedics, Inc.
N/A	LBA	74	Fox Chase Cancer Center; NCI
Oncolytic measles virus encoding thyroidal sodium iodide symporter	LBA; mesenchymal stem cell transplantation	54	Mayo Clinic; NCI
N/A	LBA; pharmacological study	96	European Organisation for Research and Treatment of Cancer (EORTC)
N/A	N/A	48	Advenchen Laboratories, LLC
N/A	N/A	190	Celldex Therapeutics; Bristol-Myers Squibb
DEC-205/NY-ESO-1 fusion protein CDX-1401	LBA; pharmacological study	98	Roswell Park Cancer Institute; NCI; Celldex Therapeutics
N/A	N/A	222	Medical University Innsbruck; European Commission
N/A	N/A	116	Eli Lilly and Company
N/A	LBA; pharmacological study	162	NCI
Enadenotucirev	N/A	35	PsiOxus Therapeutics, Ltd

NCT Number	Title	Drug Intervention
NCT02354131*	Niraparib and/or Niraparib-Bevacizumab Combination Against Bevacizumab Alone in HRD Platinum-Sensitive Ovarian Cancer	Niraparib; bevacizumab
NCT02098343*	p53 Suppressor Activation in Recurrent High-Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246	APR-246; carboplatin; pegylated liposomal doxorubicin hydrochloride
Phase II Interventional Studies		
NCT02107950	Phase II Study DCVAC/OvCa Plus Carboplatin Gemcitabine Relapsed Platinum (Pt)-Sensitive Epithelial Ovarian Carcinoma	Standard of care chemotherapy
NCT01039207	Rilotumumab in Treating Patients With Persistent or Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	N/A
NCT02107378	Efficacy of DCVAC/OvCa Plus Standard of Care in Relapsed Platinum Resistant Epithelial Ovarian Carcinoma	Standard of care (paclitaxel or topotecan or doxorubicin)
NCT01118052	EGEN-001 in Treating Patients With Persistent or Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	N/A
NCT00679783	Phase II Study of AZD2281 in Patients With Known BRCA Mutation Status or Recurrent High-Grade Ovarian Cancer or Patients With Known BRCA Mutation Status/Triple Neg Breast Cancer	AZD2281
NCT00993655	Comparing Combination Chemotherapy Regimens in Treating Patients With Stage IIB, Stage IIC, Stage III, or Stage IV Ovarian Epithelial Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer	Carboplatin; cisplatin; paclitaxel
NCT00979992	Sunitinib Malate in Treating Patients With Persistent or Recurrent Clear Cell Ovarian Cancer	Sunitinib malate

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	147	Nordic Society for Gynaecologic Oncology; ENGOT; GCIG; Stanford University
N/A	N/A	Null	Aprea AB
DCVAC/OvCa	N/A	60	Sotio a.s.
Rilotumumab	Diagnostic LBA	50	Gynecologic Oncology Group; NCI
DCVAC/OvCa	N/A	60	Sotio a.s.
EGEN-001	LBA	56	Gynecologic Oncology Group; NCI
N/A	N/A	112	AstraZeneca; British Columbia Cancer Agency
N/A	QOL assessment	275	NCIC Clinical Trials Group; NCI; Grupo Español de Investigación en Cáncer de Ovario; Cancer Research UK; Southwest Oncology Group
N/A	LBA	53	NCI

NCT Number	Title	Drug Intervention
NCT00538031	Cyclophosphamide With or Without Celecoxib in Treating Patients With Recurrent or Persistent Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cancer	Cyclophosphamide; celecoxib
NCT00278343	Cediranib Maleate in Treating Patients With Persistent, Recurrent, or Refractory Advanced Ovarian Epithelial, Peritoneal Cavity, or Fallopian Tube Cancer	Cediranib maleate
NCT02283658	Everolimus and Letrozole in Treating Patients With Recurrent Hormone Receptor Positive Ovarian, Fallopian Tube, or Primary Peritoneal Cavity Cancer	Everolimus; letrozole
NCT01666444	VTX-2337 and Pegylated Liposomal Doxorubicin (PLD) in Patients With Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer	Pegylated liposomal doxorubicin (PLD); VTX-2337
NCT00511992	Study of Bevacizumab Followed by Bevacizumab Consolidation for Ovarian Cancer	Avastin
NCT00872989	S0904: Docetaxel With or Without Vandetanib in Treating Patients With Persistent or Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Docetaxel; vandetanib
NCT01097746	First-line Treatment of Weekly Paclitaxel With Carboplatin and Bevacizumab in Ovarian Cancer	Carboplatin; paclitaxel; bevacizumab
NCT01720173	Dalantercept in Treating Patients With Recurrent Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cavity Cancer	N/A
NCT01716715	Cabozantinib or Paclitaxel in Treating Patients With Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cavity Cancer	Cabozantinib S-malate; paclitaxel
NCT01540565	Veliparib in Treating Patients With Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Veliparib
NCT01468909	Paclitaxel With or Without Pazopanib Hydrochloride in Treating Patients With Persistent or Recurrent Ovarian Epithelial, Fallopian Tube, or Peritoneal Cavity Cancer	Paclitaxel; pazopanib hydrochloride

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	27	City of Hope Medical Center
N/A	LBA	74	NCI
N/A	LBA	20	Mayo Clinic; NCI
N/A	N/A	290	VentiRx Pharmaceuticals Inc.; Gynecologic Oncology Group
N/A	N/A	22	University of Oklahoma; Genentech, Inc.
N/A	N/A	120	Southwest Oncology Group; NCI
N/A	N/A	30	MD Anderson Cancer Center; Genentech, Inc.
Dalantercept	LBA	56	Gynecologic Oncology Group; NCI
N/A	LBA	102	NCI
N/A	LBA	51	NCI
N/A	LBA	110	NCI

NCT Number	Title	Drug Intervention
NCT01305213	Bevacizumab With or Without Fosbretabulin Tromethamine in Treating Patients With Recurrent or Persistent Ovarian Epithelial, Fallopian Tube, or Peritoneal Cavity Cancer	Fosbretabulin tromethamine
NCT01199263	Paclitaxel With or Without Viral Therapy in Treating Patients With Recurrent or Persistent Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cancer	Paclitaxel
NCT01010126	Temsirolimus and Bevacizumab in Treating Patients With Advanced Endometrial, Ovarian, Liver, Carcinoid, or Islet Cell Cancer	Temsirolimus
NCT02324595	Minimally Invasive Interval Debulking Surgery in Ovarian Neoplasm: A Feasibility Study	N/A
NCT01991210	A Randomized Study of DNIB0600A in Comparison With Pegylated Liposomal Doxorubicin in Patients With Platinum-Resistant Ovarian Cancer	DNIB0600A; pegylated liposomal doxorubicin
NCT00857545	OPT-821 With or Without Vaccine Therapy in Treating Patients With Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Peritoneal Cancer in Second or Third Complete Remission	N/A
NCT00744718	Bevacizumab and Carboplatin for Patients With Ovarian Cancer	Bevacizumab; carboplatin
NCT00551070	Selumetinib in Treating Woman With Recurrent Low-Grade Ovarian Cancer or Peritoneum Cancer	Selumetinib
NCT01460979	Activity, Tolerability, Safety of Temsirolimus in Women With Ovarian Cancer Who Progressed During Previous Platinum Chemotherapy or Within 6 Months After Therapy or Advanced Endometrial Carcinoma	Temsirolimus
NCT00373217	Vaccine Therapy, Paclitaxel, and Carboplatin in Treating Patients Who Are Undergoing Surgery for Stage III or Stage IV Ovarian Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer	Carboplatin; paclitaxel

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
Bevacizumab	LBA	110	NCI
Wild-type reovirus	LBA	110	NCI
Bevacizumab	N/A	299	NCI
N/A	Laparoscopic interval debulking surgery	30	Catholic University of the Sacred Heart; Fagotti, Anna, M.D.; Francesco Fanfani; Salvatore Gueli Alletti
N/A	N/A	95	Genentech, Inc.
Immunoadjuvant OPT-821; polyvalent antigen-KLH conjugate vaccine	LBA	164	Gynecologic Oncology Group; NCI
N/A	N/A	30	Vejle Hospital
N/A	LBA; pharmacological study	52	NCI
N/A	N/A	86	AGO Study Group
MAGE-A1, Her-2/neu, FBP peptides ovarian cancer vaccine; tetanus toxoid helper peptide	Conventional surgery	28	Craig L Slingluff, Jr.; NCI; University of Virginia

NCT Number	Title	Drug Intervention
NCT01551745	Salvage Ovarian FANG™ Vaccine + Bevacizumab	Bevacizumab
NCT01439659	Juice Plus+ and Juice Plus+ Complete in Ovarian Cancer	N/A
NCT01309230	Trial of Adjuvant FANG™ Vaccine for High-Risk Stage III/IV Ovarian Cancer	N/A
NCT02435186*	p53 Gene in Treatment of Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer	p53 gene; cisplatin; paclitaxel
NCT02107937*	Phase II Study DCVAC/OvCa Added to First-Line Carboplatin and Paclitaxel Newly Diagnosed Epithelial Ovarian Carcinoma	Standard of care
NCT01764802*	Psychosexual Intervention in Patients With Stage I–III Gynecologic or Breast Cancer	N/A
NCT02122185*	Metformin Hydrochloride and Combination Chemotherapy in Treating Patients With Stage III–IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Paclitaxel; carboplatin; docetaxel; metformin hydrochloride
NCT00888615*	Elesclomol Sodium and Paclitaxel in Treating Patients With Recurrent or Persistent Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Elesclomol sodium; paclitaxel
NCT02584465*	REGorafenib vs. Tamoxifen in Patients With Platinum-Sensitive Ovarian Carcinoma and Isolated Biological Progression	Tamoxifen; regorafenib
NCT02487849*	HIPEC After Secondary Cytoreductive Operation in Patients With Platinum-Sensitive Recurrence of Ovarian Carcinoma	Carboplatin
NCT01899599*	PankoMab-GEX™ Versus Placebo as Maintenance Therapy in Advanced Ovarian Cancer	PankoMab-GEX
NCT02033616*	Autologous Dendritic Cell-Tumor Cell Immunotherapy for Advanced Epithelial Ovarian Carcinomas	N/A
NCT02487693*	Radiofrquency Ablation Combined With Cytokine-induced Killer Cells for Patients With Ovarian Carcinoma	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
Vigil™ vaccine	N/A	5	Gradalis, Inc.
N/A	Nutritional counseling; daily supplements	75	MD Anderson Cancer Center; Natural Alternatives International
Vigil™	N/A	44	Gradalis, Inc.
N/A	N/A	100	Shenzhen SiBiono; GeneTech Co., Ltd.
DCVAC/OvCa	N/A	90	Sotio a.s.
N/A	Behavioral, psychological, or informational intervention	100	Ohio State University Comprehensive Cancer Center; NCI
N/A	LBA	160	University of Chicago; NCI
N/A	N/A	55	Gynecologic Oncology Group; NCI
N/A	N/A	116	ARCAGY/GINECO GROUP; Bayer
N/A	HIPEC	10	Krankenhaus Barmherzige Schwestern Linz
N/A	N/A	210	Glycotope GmbH
Ovapuldencel-T; MC: autologous PBMCs in GM-CSF	N/A	99	Caladrius Biosciences, Inc.
Cytokine-induced killer cells	Radiofrequency ablation	50	The First People's Hospital of Changzhou

NCT Number	Title	Drug Intervention
NCT02437812*	Study of Paclitaxel, Carboplatin, and Oral Metformin in the Treatment of Advanced-Stage Ovarian Carcinoma	Metformin; paclitaxel; carboplatin
NCT01735071*	Bevacizumab and Trabectedin +/– Carboplatin in Advanced Ovarian Cancer	Bevacizumab; trabectedin; carboplatin
NCT02315430*	Cabozantinib-S-Malate in Treating Patients With Recurrent or Progressive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Cabozantinib S-malate
NCT02569957*	Effect of Acetylcysteine With Topotecan Hydrochloride on the Tumor Microenvironment in Patients With Persistent or Recurrent High-Grade Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Topotecan hydrochloride; acetylcysteine
NCT02124421*	Outcomes in CRS/HIPEC as Initial Treatment of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	Adjuvant chemotherapy; carboplatin; paclitaxel; cisplatin
NCT02364713*	MV-NIS or Investigator's Choice Chemotherapy in Treating Patients With Ovarian, Fallopian, or Peritoneal Cancer	Pegylated liposomal doxorubicin hydrochloride; gemcitabine hydrochloride; topotecan hydrochloride; paclitaxel
NCT02101775*	Gemcitabine Hydrochloride With or Without WEE1 Inhibitor MK-1775 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Gemcitabine hydrochloride; WEE1 inhibitor AZD1775
NCT02125513*	Neoadjuvant Chemotherapy in Epithelial Ovarian Cancer	Carboplatin; paclitaxel
NCT02025985*	Phase II Study of KPT-330 (Selinexor) in Female Patients With Advanced Gynaecologic Malignancies & Metastatic Breast Cancer	Selinexor

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	30	Gynecologic Oncology Associates; University of North Carolina at Chapel Hill
N/A	N/A	74	Mario Negri Institute for Pharmacological Research; PharmaMar; Hoffmann-La Roche
N/A	LBA	34	NCI
N/A	N/A	48	Thomas Jefferson University; NIH
N/A	Cytoreductive surgery; questionnaire; HIPEC	48	Mercy Medical Center
Oncolytic measles virus encoding thyroidal sodium iodide symporter	LBA; QOL assessment	134	Mayo Clinic; NCI
N/A	LBA; pharmacological study	100	NCI
N/A	Surgery	220	Azienda Ospedaliera Universitaria di Bologna Policlinico S. Orsola Malpighi
N/A	N/A	105	Karyopharm Therapeutics, Inc.

NCT Number	Title	Drug Intervention
NCT01936974*	(PGA) for Platinum-Resistant/Refractory, Paclitaxel-Pretreated Recurrent Ovarian and Peritoneal Carcinoma	Gemcitabine; bevacizumab; carboplatin; cisplatin; oxaliplatin
NCT02595021*	Total/Subtotal Colectomy in Ovarian Cancer	N/A
NCT01891344*	A Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2)	Oral rucaparib
NCT01536743*	A Open Label Study of the Efficacy and Safety of PD0332991 a Selective Inhibitor of the Cyclin Dependent Kinases 4 and 6 in Patients With Recurrent Ovarian Cancer Demonstrating Rb-proficiency and Low p16 Expression	PD0332991
NCT02595892*	Gemcitabine Hydrochloride Alone or With VX-970 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	ATR kinase inhibitor VX-970; gemcitabine hydrochloride
NCT02345265*	Olaparib and Cediranib Maleate in Treating Patients With Recurrent Ovarian, Peritoneal, or Fallopian Tube Cancer	Cediranib maleate; olaparib
NCT02312245*	Avatar-Directed Chemotherapy in Treating Patients With Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Gemcitabine hydrochloride; paclitaxel; pegylated liposomal doxorubicin hydrochloride; topotecan hydrochloride
NCT02059265*	Dasatinib in Treating Patients With Recurrent or Persistent Ovarian, Fallopian Tube, Endometrial, or Peritoneal Cancer	Dasatinib
NCT01853644*	Tivozanib in Recurrent, Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Tivozanib

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	88	Western Regional Medical Center
N/A	Total or subtotal colectomy; other bowel resection	80	Shanghai Gynecologic Oncology Group; Shanghai Zhongshan Hospital
N/A	N/A	480	Clovis Oncology, Inc.; Foundation Medicine
N/A	N/A	30	Jonsson Comprehensive Cancer Center
N/A	LBA	70	NCI
N/A	LBA; pharmacological study	70	NCI
N/A	N/A	60	Mayo Clinic; NCI
N/A	LBA	62	NCI
N/A	N/A	30	Northwestern University; National Comprehensive Cancer Network

NCT Number	Title	Drug Intervention
NCT01669226*	First-line Intraperitoneal Cisplatin and Etoposide Chemotherapy for Ovarian Cancer	PEip (weekly) and TCiv; TCiv
NCT01669798*	BIBF 1120 in Bevacizumab Resistant, Persistent, or Recurrent Epithelial Ovarian Cancer	BIBF 1120
NCT02135523*	The Efficacy of Involved-field Radiation Therapy for Residual or Locoregionally Recurrent Epithelial Ovarian Cancer After Definitive Treatment; Multi-institutional Clinical Trial	N/A
NCT02435186*	p53 Gene in Treatment of Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer	p53 gene; cisplatin; paclitaxel
NCT02487849*	HIPEC After Secondary Cytoreductive Operation in Patients With Platinum-Sensitive Recurrence of Ovarian Carcinoma	Carboplatin
NCT02033616*	Autologous Dendritic Cell-Tumor Cell Immunotherapy for Advanced Epithelial Ovarian Carcinomas	N/A
NCT02631876*	PH2 Study of IMGN853 vs. Investigator's Choice of Chemo in Adults With FRa+ Adv. EOC, Primary Peritoneal, or Primary Fallopian Tube Cancer	IMGN853; paclitaxel; doxorubicin; gemcitabine; topotecan
NCT02487693*	Radiofrquency Ablation Combined With Cytokine-Induced Killer Cells for the Patients With Ovarian Carcinoma	N/A
NCT02627443*	Carboplatin and Gemcitabine Hydrochloride With or Without ATR Kinase Inhibitor VX-970 in Treating Patients With Recurrent and Metastatic Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	ATR kinase inhibitor VX-970; carboplatin; gemcitabine hydrochloride
NCT02595892*	Gemcitabine Hydrochloride Alone or With VX-970 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	ATR kinase inhibitor VX-970; gemcitabine hydrochloride

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	N/A	200	Shanghai Gynecologic Oncology Group; Fudan University; Shanghai Jiao Tong University School of Medicine; Shanghai Zhongshan Hospital
N/A	N/A	56	AA Secord; Boehringer Ingelheim; Duke University
N/A	Involved-field radiation therapy	70	Yonsei University
N/A	N/A	100	Shenzhen SiBiono GeneTech Co., Ltd.
N/A	HIPEC	10	Krankenhaus Barmherzige Schwestern Linz
Ovapuldencel-T; MC: autologous PBMCs in GM-CSF	N/A	99	Caladrius Biosciences, Inc.
N/A	N/A	247	ImmunoGen, Inc.
Cytokine-induced killer cells	Radiofrequency ablation	50	The First People's Hospital of Changzhou
N/A	LBA; pharmacological study	117	NCI
N/A	LBA	70	NCI

NCT Number	Title	Drug Intervention
Phase II/III Interventional Studies		
NCT02101788*	Trametinib in Treating Patients With Recurrent or Progressive Low-Grade Ovarian Cancer or Peritoneal Cavity Cancer	Letrozole; paclitaxel; pegylated liposomal doxorubicin hydrochloride; tamoxifen citrate; topotecan hydrochloride; trametinib
NCT02502266*	Cediranib Maleate and Olaparib or Standard Chemotherapy in Treating Patients With Recurrent Platinum-Resistant or -Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Cediranib maleate; olaparib; paclitaxel; pegylated liposomal doxorubicin hydrochloride; topotecan hydrochloride
NCT01506856*	Intraperitoneal Therapy for Ovarian Cancer With Carboplatin Trial	IV paclitaxel + IV carboplatin; IV paclitaxel + IP carboplatin
Phase III Interventional Studies		
NCT00951496	Bevacizumab and Intravenous or Intraperitoneal Chemotherapy in Treating Patients With Stage II–III Ovarian Epithelial Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Carboplatin; cisplatin; paclitaxel
NCT01167712	Paclitaxel and Carboplatin With or Without Bevacizumab in Treating Patients With Stage II, Stage III, or Stage IV Ovarian Epithelial Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer	Carboplatin; paclitaxel
NCT01081262	Carboplatin and Paclitaxel or Oxaliplatin and Capecitabine With or Without Bevacizumab as First-Line Therapy in Treating Patients With Newly Diagnosed Stage II–IV or Recurrent Stage I Epithelial Ovarian or Fallopian Tube Cancer	Capecitabine; carboplatin; oxaliplatin; paclitaxel
NCT00954174	Paclitaxel and Carboplatin or Ifosfamide in Treating Patients With Newly Diagnosed Persistent or Recurrent Uterine, Ovarian, Fallopian Tube, or Peritoneal Cavity Cancer	Paclitaxel; carboplatin; ifosfamide

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	LBA; pharmacological study; QOL assessment	250	NCI
N/A	LBA; questionnaire administration	680	NCI
N/A	N/A	654	Gynecologic Oncology Trial & Investigation Consortium; Japanese Gynecologic Oncology Group
Bevacizumab	LBA; QOL assessment	1500	NCI
Bevacizumab	Computed tomography; therapeutic conventional surgery	650	NCI
Bevacizumab	LBA; QOL assessment	332	NCI
N/A	QOL assessment	603	Gynecologic Oncology Group; NCI

NCT Number	Title	Drug Intervention
NCT00108745	Paclitaxel or Polyglutamate Paclitaxel or Observation in Treating Patients With Stage III or Stage IV Ovarian Epithelial or Peritoneal Cancer or Fallopian Tube Cancer	Paclitaxel poliglumex; paclitaxel
NCT00305851	Music Therapy or Book Discussion in Improving Quality of Life in Young Patients Undergoing Stem Cell Transplant	N/A
NCT01684878	A Study of Pertuzumab in Combination With Standard Chemotherapy in Women With Recurrent Platinum-Resistant Epithelian Ovarian Cancer and Low HER3 mRNA Expression	Chemotherapy; pertuzumab
NCT01376349	Prasterone (Dehydroepiandrosterone) in Treating Postmenopausal Cancer Survivors With Vaginal Symptoms	Prasterone
NCT01837251	Evaluation of Optimal Treatment With Bevacizumab in Patients With Platinum-Sensitive Recurrent Ovarian Cancer	Carboplatin; PLD
NCT01462890	Evaluation of Optimal Initial Treatment Duration of Bevacizumab in Combination With Standard Chemotherapy in Patients With Ovarian Cancer	Paclitaxel; carboplatin
NCT01281254	AMG 386 (Trebananib) in Ovarian Cancer (TRINOVA-2)	AMG386; PLD
NCT00719303*	Diet and Physical Activity Change or Usual Care in Improving Progression-Free Survival in Patients With Previously Treated Stage II, III, or IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Clinical observation	1,100	Gynecologic Oncology Group; NCI
N/A	Music therapy (books on tape); psychosocial assessment and care; QOL assessment; music video	118	Children's Oncology Group; NCI; National Institute of Nursing Research (NINR)
N/A	N/A	208	Hoffmann-La Roche
N/A	N/A	464	Alliance for Clinical Trials in Oncology; NCI; Mayo Clinic
Bevacizumab	N/A	682	AGO Research GmbH; Arbeitsgemeinschaft Gynaekologische Onkologie Austria; ARCAGY/ GINECO GROUP; ANZGOG; Scottish Gynaecological Cancer Study Group
Bevacizumab	Specialized pathology review E182 (Germany only)	800	AGO Study Group; ARCAGY/ GINECO GROUP; Nordic Society for Gynaecologic Oncology
N/A	N/A	223	Amgen
N/A	Behavioral dietary intervention; compliance monitoring; counseling; educational intervention; exercise intervention; LBA; QOL assessment; questionnaire administration	1,070	Gynecologic Oncology Group; NCI

NCT Number	Title	Drug Intervention
NCT01628380*	Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer	N/A
NCT00426257*	Secondary Debulking Surgery +/– Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer	N/A
NCT01802749*	Bevacizumab Beyond Progression in Platinum-Sensitive Ovarian Cancer	Bevacizumab; paclitaxel; carboplatin; pegylated liposomal doxorubicin; gemcitabine
NCT01654146*	ICON8: Weekly Chemotherapy in Ovarian Cancer	Carboplatin; paclitaxel
NCT01846611*	A Study Comparing the Combination of Trabectedin (YONDELIS) and DOXIL/ CAELYX With DOXIL/CAELYX for the Treatment of Advanced-Relapsed Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Trabectedin; DOXIL; dexamethasone
NCT00565851*	Carboplatin, Paclitaxel, and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer	Carboplatin; docetaxel; gemcitabine hydrochloride; paclitaxel
NCT01611766*	Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC 1 Trial)?	Salvage chemotherapy
NCT01376752*	Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Cytoreductive surgery and HIPEC; cytoreductive surgery alone	94	A.O. Ospedale Papa Giovanni XXIII; Clinical Organization for Strategies & Solutions (CLIOSS), former Nerviano Medical Sciences; Onlus Cancro Primo Aiuto
N/A	Secondary debulking with or without IP chemotherapy	280	The Netherlands Cancer Institute
N/A	N/A	400	National Cancer Institute, Naples; Mario Negri Institute for Pharmacological Research
N/A	N/A	1,485	Medical Research Council; Cancer Research UK
N/A	N/A	670	Janssen Research & Development, LLC; PharmaMar
Bevacizumab	LBA; QOL assessment	1,038	NCI
N/A	Secondary cytoreductive surgery	420	Shanghai Gynecologic Oncology Group; Fudan University; Zhejiang Cancer Hospital; Shanghai Zhongshan Hospital; Sun Yat-sen University
N/A	Maximal cytoreductive surgery	444	UNICANCER

NCT Number	Title	Drug Intervention
NCT02446600*	Olaparib or Cediranib Maleate and Olaparib Compared With Standard Platinum-Based Chemotherapy in Treating Patients With Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Carboplatin; cediranib maleate; gemcitabine hydrochloride; olaparib; paclitaxel; pegylated liposomal doxorubicin hydrochloride
Phase IV Interventional Studies		
NCT01706120	Study of Clinical and Biological Prognostic Factors in Patients With Ovarian Cancer Receiving Carboplatin + Paclitaxel With Bevacizumab	Bevacizumab; paclitaxel; carboplatin
Interventional Studies (Phase Not Indicated)		
NCT01747798	Auranofin in Treating Patients With Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Auranofin
NCT02096783	Scripted Sexual Health Informational Intervention in Improving Sexual Function in Patients With Gynecologic Cancer	N/A
NCT01696994	Screening for Ovarian Cancer in Older Patients (PLCO Screening Trial)	N/A
NCT02595281	HE4 as a Relapse Biomarker in Ovarian Cancers	N/A
NCT00946283	Lactobacillus in Preventing Infection in Patients Undergoing a Donor Stem Cell Transplant for Hematologic Cancer or Myelodysplastic Syndrome	N/A
NCT02578888*	Palliative Care in Improving QOL in Patients With High-Risk Primary or Recurrent Gynecologic Malignancies	N/A
NCT02013492*	Propranolol Hydrochloride in Treating Patients With Locally Recurrent or Metastatic Solid Tumors That Cannot Be Removed by Surgery	Propranolol hydrochloride
NCT01442051*	Acute Normovolemic Hemodilution in Patients Undergoing Cytoreductive Surgery for Advanced Ovarian Cancer	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	LBA; QOL assessment	450	NCI
N/A	N/A	400	National Cancer Institute, Naples; Mario Negri Institute for Pharmacological Research
N/A	LBA	10	Mayo Clinic
N/A	Informational intervention; counseling intervention; questionnaire administration	30	University of Wisconsin–Madison; NCI
N/A	Ultrasound imaging; screening questionnaire administration; LBA	78,216	NCI
N/A	Experimental arm	90	Institut de Cancérologie de Lorraine
N/A	Lactobacillus rhamnosus GG (dietary supplement)	30	Rutgers, The State University of New Jersey; NCI; Rutgers Cancer Institute of New Jersey
N/A	Palliative therapy; palliative therapy + idiographic	180	Albert Einstein College of Medicine of Yeshiva University; NCI
N/A	Correlative studies	35	William Carson; Ohio State University Comprehensive Cancer Center
N/A	Acute normovolemic hemodilution	41	Memorial Sloan Kettering Cancer Center

NCT Number	Title	Drug Intervention
NCT02530606*	Photoacoustic Imaging in Detecting Ovarian or Fallopian Tube Cancer	N/A
NCT02412124*	Peer-to-Peer Support Program in Improving QOL Outcomes in Patients With Gynecologic Cancer and Their Caregivers	N/A
NCT02218502*	Study Into a New Diagnostic Tool (Simple Ultrasound-based Rules) in Patients With Adnexal Masses	N/A
NCT01519869*	Trial of Chemotherapy in Ovarian, Fallopian Tube and Peritoneal Carcinoma	Neoadjuvant chemotherapy
NCT02477202*	Mirena® Intra-Uterine Device's (IUD's) Effect on Fallopian Tube Fimbriae and Ovarian Cortical Inclusion Cyst Cell Proliferation	N/A
NCT01230346*	Culturally-Informed Counseling in Latinas at High Risk for Hereditary Breast or Ovarian Cancer	N/A
NCT02281487*	Hysterectomy for Benign Gynaecological Conditions With or Without Tubectomy	N/A
NCT01504126*	Feasibility Study: Therapeutic Targeting of Stress Factors in Ovarian Cancer Patients	Propranolol; chemotherapy
NCT02530606*	Photoacoustic Imaging in Detecting Ovarian or Fallopian Tube Cancer	N/A
NCT02110277*	Photoacoustic Imaging of the Ovary	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Photoacoustic imaging	20	Stanford University; NCI
N/A	Supportive care; QOL assessment; questionnaire administration	30	City of Hope Medical Center; NCI
N/A	Ultrasound by general gynaecologist; ultrasound by an expert ultrasonographist; DW-MRI; give blood sample	270	Maastricht University Medical Center; Laurentius Hospital Roermond; St. Jans Gasthuis Weert; VieCuri Medical Centre; Orbis Medical Centre
N/A	N/A	28	Rachel Miller; University of Kentucky
N/A	Mirena® IUD	14	Memorial Sloan Kettering Cancer Center
N/A	Questionnaire administration; survey administration; counseling intervention; educational intervention	475	City of Hope Medical Center; NCI
N/A	Hysterectomy with or without tubectomy; light microscopy	100	Gynaecologisch Oncologisch Centrum Zuid; St. Elisabeth Hospital, Tilburg, Netherlands; Catharina Ziekenhuis Eindhoven; Radboud University; Jeroen Bosch Ziekenhuis
N/A	Surgery; questionnaire	25	MD Anderson Cancer Center; Sprint for Life
N/A	Photoacoustic imaging	20	Stanford University; NCI
N/A	Photoacoustic imaging/ ultrasound diagnostic group (device)	40	University of Connecticut Health Center; NCI

NCT Number	Title	Drug Intervention
NCT01846520*	Family Caregiver Palliative Care Intervention in Supporting Caregivers of Patients With Stage II–IV Gastrointestinal, Gynecologic, and Urologic Cancers	N/A
NCT02082470*	Survivorship Care Planning in Improving QOL in Survivors of Ovarian Cancer	N/A
NCT02323568*	Live After an Epithelial Ovarian Cancer: Multidisciplinary Assessment of Effects and Long-term Remission in Patients Needs	N/A
NCT02111941*	Vaccine Therapy in Treating Patients With Stage IIIC–IV Ovarian Epithelial, Fallopian Tube, or Primary Peritoneal Cavity Cancer Following Surgery and Chemotherapy	N/A
NCT02039388*	Lavage of the Uterine Cavity for the Diagnosis of Serous Tubal Intraepithelial Carcinoma	N/A
NCT02376231*	To Evaluate Plasmajet in Achieving Complete Cytoreduction of Advanced EOC–Initial Feasibility Study	N/A
NCT02518256*	Lavage of the Uterine Cavity for the Diagnosis of Ovarian and Tubal Carcinoma–Study of Sensitivity and Specificity	N/A
NCT02062697*	Lavage of the Uterine Cavity for the Diagnosis of Ovarian and Tubal Carcinoma and Their Premalignant Changes	N/A
Observational Studies		
NCT01276574	Epithelial Ovarian Cancer–Staging and Response to Chemotherapy Evaluated by PET/CT	Not indicated
NCT00899093	Tumor Marker YKL-40 in Patients With Newly Diagnosed Stage III or Stage IV Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer Undergoing Chemotherapy	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Educational intervention; telephone-based intervention; QOL assessment; questionnaire administration	200	City of Hope Medical Center; NCI; American Cancer Society National Office
N/A	Follow-up care; active surveillance; questionnaire administration	20	City of Hope Medical Center; NCI
N/A	Gynecological consultation	120	Centre Francois Baclesse; Ligue contre le cancer, France; Fondation de France
Multi-epitope folate receptor alpha-loaded dendritic cell vaccine	LBA	22	Mayo Clinic; NCI
N/A	Lavage of the cavum uteri and proximal fallopian tubes	200	Medical University of Vienna
N/A	Surgery for EOC with trial (PJ) device (PlasmaJet)	150	Thumuluru Kavitha Madhuri; Royal Surrey County Hospital; NHS Foundation Trust
N/A		540	Medical University of Vienna
N/A	Lavage of the cavum uteri and proximal fallopian tubes; liquid-PAP smear	50	Medical University of Vienna
Not indicated	Not indicated	150	Turku University Hospital
N/A	LBA	2,500	Gynecologic Oncology Group; NCI

NCT Number	Title	Drug Intervention
NCT01080521	Changes in Brain Function in Patients With Stage I, Stage II, Stage III, or Stage IV Ovarian, Primary Peritoneal, or Fallopian Tube Cancer Who Are Receiving Chemotherapy	N/A
NCT01295489	Biomarkers in Patients With Previously Untreated Invasive Ovarian Epithelial, Fallopian Tube, or Peritoneal Cancer	IP chemotherapy
NCT00337233	Yoga in Controlling Symptoms and Reducing Stress in Women With Ovarian Cancer or Breast Cancer	N/A
NCT00651716	T Cells in Predicting Acute Graft-Versus-Host Disease in Patients Undergoing Donor Stem Cell Transplant	N/A
NCT00899496	Laboratory Assay in Determining Cancer Resistance in Patients With Metastatic Cancer and in Healthy Participants	N/A
NCT02297958*	Impact of Fas/FasL in Chemotherapy Response in Epithelial Ovarian Carcinoma	Not indicated
NCT02524808*	Prospective Identification and Validation of “BRCANess” Profile in Ovarian Epithelial Cancer	Not indicated
NCT00488878*	Data Collection for Patients With Low-Grade Ovarian Carcinoma	N/A
NCT01907789*	Prophylactic Salpingectomy With Delayed Oophorectomy	N/A
NCT01000259*	Study of Tumor Tissue Samples From Patients Who Have Undergone Surgery for Advanced Stage III or Stage IV Ovarian Epithelial Cancer	N/A

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
N/A	Cognitive assessment; QOL assessment	256	Gynecologic Oncology Group; NCI
N/A	Gene expression analysis; protein analysis; flow cytometry; immunoenzyme technique; immunohistochemistry staining method; LBA	39	Gynecologic Oncology Group; NCI
N/A	Yoga therapy	106	Comprehensive Cancer Center of Wake Forest University; NCI
N/A	Flow cytometry; LBA; data collection	200	Vanderbilt-Ingram Cancer Center; NCI; NIH
N/A	Immunological diagnostic method; physiologic testing	48	Comprehensive Cancer Center of Wake Forest University; NCI
Not Indicated	Not indicated	40	Rennes University Hospital
Not Indicated	Not indicated	230	Fundación de investigación HM; AstraZeneca
N/A	Data collection	2,000	MD Anderson Cancer Center
N/A	Ovarian cancer screening; prophylactic salpingectomy with delayed oophorectomy; risk-reducing salpingo-oophorectomy; questionnaire; transvaginal ultrasound; phone call	80	MD Anderson Cancer Center
N/A	LBA	174	Gynecologic Oncology Group; NCI

NCT Number	Title	Drug Intervention
NCT00628654*	Glycan Analysis in Diagnosing Cancer in Women With Ovarian Epithelial Cancer and in Healthy Female Participants	Not indicated
NCT02315469*	Comprehensive Patient Questionnaires in Predicting Complications in Older Patients With Gynecologic Cancer Undergoing Surgery	N/A
NCT01832415*	First-Line Ovarian Cancer Treatment–Cohort Study	Bevacizumab
NCT02394015*	Retrospective Study to Analyze the Efficacy and Safety of Trabectedin and Pegylated Liposomal Doxorubicin (PLD) in the Treatment of Patients With Platinum-sensitive Recurrent Ovarian Cancer (ROC), According to SmPC	Trabectedin and pegylated liposomal doxorubicin
NCT01445275*	Cost of Cancer Risk Management in Women at Elevated Genetic Risk for Ovarian Cancer Who Participated on GOG-0199	N/A
NCT02073500*	Peritoneal Surface Malignancies–Characterization, Models and Treatment Strategies	N/A
NCT02489058*	A Study of Long-Term Responders on Olaparib	Not indicated
NCT02291276*	Perioperative Assessment of Right Ventricular Function and Venous Return in Patients With Epithelial Ovarian Cancer Undergoing Cytoreductive Surgery (Gyn Right)–Pilot Study	Not indicated
NCT01932125*	An Observational Study of Avastin (Bevacizumab) in Patients With Advanced/Metastatic Epithelial Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	Not indicated
NCT02408536*	Observational Retrospective Study on Treatment and Outcomes in Patients With Low-Grade Serous Ovarian Cancer	Not indicated
NCT01703442*	Intraoperative Anuric Episodes in Patients Undergoing Laparotomy	Not indicated

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
Not indicated	Not indicated	700	University of California, Davis; NCI
N/A	Comprehensive geriatric assessment; questionnaire administration	228	NRG Oncology; NCI
N/A	N/A	500	ARCAGY/ GINECO GROUP; Roche Pharma AG
N/A	N/A	80	Grupo Español de Investigación en Cáncer de Ovario; PharmaMar
N/A	Evaluation of cancer risk factors; medical chart review; study of socioeconomic and demographic variables	2,605	Gynecologic Oncology Group; NCI
N/A	Observational study	200	Oslo University Hospital; The Research Council of Norway
Not indicated	Not indicated	100	University Health Network, Toronto
Not indicated	Not indicated	30	Charite University, Berlin, Germany
Not indicated	Not indicated	100	Hoffmann-La Roche
Not indicated	Not indicated	150	National Cancer Institute, Naples
Not indicated	Not indicated	25	Claudia Spies; Charite University, Berlin, Germany

NCT Number	Title	Drug Intervention
NCT01982500*	Observation of Bevacizumab Plus Front-Line Chemotherapy in Patients With Ovarian Cancer	Not indicated
NCT00005095*	Specimen and Data Study for Ovarian Cancer Early Detection and Prevention	N/A
NCT02524808*	Prospective Identification and Validation of "BRCANess" Profile in Ovarian Epithelial Cancer	Not indicated
NCT02489058*	A Study of Long-Term Responders on Olaparib	Not indicated
NCT01703442*	Intraoperative Anuric Episodes in Patients Undergoing Laparotomy	Not indicated

Biological Intervention	Other Intervention	Estimated Enrollment	Sponsor/ Collaborators
Not indicated	Not indicated	200	Hellenic Oncology Research Group
N/A	LBA; screening questionnaire administration; study of high-risk factors	6000	Northwestern University; NCI
Not indicated	Not indicated	230	Fundación de investigación HM; AstraZeneca
Not indicated	Not indicated	100	University Health Network, Toronto
Not indicated	Not indicated	25	Claudia Spies; Charite University, Berlin, Germany

Appendix D

Workshop Agendas

JANUARY 8, 2015

The Keck Center of the National Academies
500 Fifth Street, NW,
Washington, DC 20001

1:00 p.m. **Welcome study sponsors and introductory remarks**
Jerome F. Strauss III (*Committee Chair*)
Virginia Commonwealth University School of Medicine

Lisa Richardson
Centers for Disease Control and Prevention

Discussion and Q&A

2:00 p.m. **Invited statements from stakeholders**
Calaneet Balas
Ovarian Cancer National Alliance

Comments from other public attendees

2:30 p.m. **Summary and adjournment of public session**

APRIL 7, 2015

The Keck Center of the National Academies
500 Fifth Street, NW,
Washington, DC 20001

8:45 a.m. **Welcome and opening remarks; introduction of committee**
Jerome F. Strauss III (*Committee Chair*)
Virginia Commonwealth University School of Medicine

TOPIC #1: THE BIOLOGY OF OVARIAN CANCER

9:00 a.m. **Introductions**
Douglas A. Levine (*Moderator*)
Memorial Sloan Kettering Cancer Center

9:05 a.m. **Series of presentations**

Cell of origin: Stem cells
Alexander Nikitin
Cornell University

Cell of origin: Fallopian tubes
Ronny Drapkin
University of Pennsylvania

Genetics/Single-Nucleotide Polymorphisms
Simon Gayther
University of Southern California

9:50 a.m. **Discussion with committee**

TOPIC #2: SCREENING AND EARLY DETECTION

10:50 a.m. **Introductions**
Shelley S. Tworoger (*Moderator*)
Harvard Medical School/Harvard School of Public Health/
Brigham and Women's Hospital

10:55 a.m. **Series of presentations**

Risk factors and biomarkers by histologic subtypes
Nicolas Wentzensen
National Cancer Institute

Imaging-based diagnostics for early detection
Martin McIntosh
Fred Hutchinson Cancer Research Center

Design of screening trials
Christine Berg
Johns Hopkins Medicine

11:40 a.m. **Discussion with committee**

TOPIC #3: NOVEL TREATMENTS

1:15 p.m. **Introductions**
Anil K. Sood (*Moderator*)
The University of Texas MD Anderson Cancer Center

1:20 p.m. **Series of presentations**

Challenges of development of novel therapeutics in ovarian cancer
Tony Ho
AstraZeneca

Nonpharmacologic approaches
Melinda Irwin
Yale University

Targeting p53
Guillermina Lozano
The University of Texas MD Anderson Cancer Center

2:05 p.m. **Discussion with committee**

TOPIC #4: SURVIVORSHIP

3:00 p.m. **Introductions**
Heidi Donovan (*Moderator*)
University of Pittsburgh School of Nursing

3:05 p.m. **Series of presentations**

Biobehavioral pathways in epithelial ovarian cancer
Susan Lutgendorf
University of Iowa

Quality of life and supportive care
Lari Wenzel
University of California, Irvine

Dissemination and implementation of evidence-based strategies
Karen Emmons
Kaiser Permanente

3:50 p.m. **Discussion with committee**

4:30 p.m. **Open comment period**

5:00 p.m. **Adjourn**

Appendix E

Committee and Staff Biographies

Jerome F. Strauss III, M.D., Ph.D. (*Chair*), is the dean of the Virginia Commonwealth University (VCU) School of Medicine, professor in the Department of Obstetrics and Gynecology, and executive vice president for Medical Affairs of the VCU Health System. His research interests are in the field of reproductive medicine focusing on the genetics of disorders affecting fertility and pregnancy outcome. He has authored more than 300 original scientific articles, and holds 12 issued U.S. patents for discoveries in diagnostics and therapeutics. Dr. Strauss's honors include election to Alpha Omega Alpha Honor Medical Society (1971); the University of Pennsylvania's Berwick Award for Teaching (1983); the Medical Student Government Award for Distinguished Teaching from the University of Pennsylvania (1983); the President's Achievement Award (1990) and the Distinguished Scientist Award (2006) from the Society for Gynecologic Investigation, of which he is past president (2004); the Society for the Study of Reproduction Research Award (1992); election to the National Academy of Medicine, National Academy of Sciences (1994); the Transatlantic Medal of the British Endocrine Society (1994); the Beacon (2001), Pioneer (2004), and National Research Distinguished Service Awards (2007) for contributions to the reproductive sciences; the 2005 Distinguished Graduate Award from the University of Pennsylvania School of Medicine, the highest honor that the School of Medicine bestows upon an alumnus; Chuenkong Scholar from the China Ministry of Education (2006); the Rector's Medal from the University of Chile (2009) for contributions to research and research training; and honorary professor at Wuhan University of Science and Technology, Wuhan, Hubei, China (2013). Currently, Dr. Strauss is chair, Board of

Scientific Counselors, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Ronald D. Alvarez, M.D., M.B.A., is professor and Ellen Gregg Shook Culverhouse Chair of the Division of Gynecologic Oncology at the University of Alabama at Birmingham (UAB). His long-term research interests have included the development of novel therapeutics for ovarian cancer and new screening and prevention strategies for cervical cancer. He has been the recipient of several National Cancer Institute (NCI) and other industry-funded grants in support of his research in gene therapeutics for ovarian and cervical cancer, including funded projects in the previously funded UAB Ovarian Cancer Specialized Program of Research Excellence (SPORE) and the currently funded Johns Hopkins/UAB Cervical SPORE. He has served on study sections for the NCI Clinical Oncology Section and the U.S. Department of Defense's (DoD's) Ovarian Cancer Research Program. He currently serves as co-chair of the NRG Oncology Gynecologic Committee and has served on the editorial board of *Gynecologic Oncology*. He served as president of the Society of Gynecologic Oncology in 2013 and he is currently director of the gynecologic oncology division of the American Board of Obstetrics and Gynecology.

Deborah J. Bowen, Ph.D., is a professor in the Department of Bioethics and Humanities at the University of Washington. She was recently a professor and chair in the Department of Community Health Sciences of the School of Public Health at Boston University (BU). She has been the principal investigator of several National Institutes of Health (NIH)-funded grants involving breast/ovarian cancer and melanoma risk feedback and communications, including the Breast Cancer Risk Counseling Studies, the RISK study, and the WIRES and Suntalk studies. Dr. Bowen has been an investigator in the coordinating centers of three large multicenter prevention trials: the Carotene and Retinol Efficacy Trial (CARET), the Women's Health Trial: Feasibility Study in Minority Populations (WHT:FSMP), and the Women's Health Initiative (WHI). She is currently conducting community-based research to improve the health of native people in the Pacific Northwest and Alaska, in collaboration with community partners. She was the director of the Prevention Research Center at BU, focused on improving the health of public housing residents. In addition, Dr. Bowen has led or participated in numerous community intervention studies that have successfully recruited and maintained advisory committees, including members of the community representing the target audience. She was a co-investigator and member of the steering committee for a large R25T training grant for pre- and post-doctoral fellows at the University of Washington, focused on health communications and biobehavioral cancer prevention.

Kathleen R. Cho, M.D., is the Peter A. Ward Professor and vice chair for Academic Affairs in the Department of Pathology at the University of Michigan Medical School. Dr. Cho is an actively practicing surgical pathologist with a substantial schedule of consults and in-house cases in diagnostic pathology. She serves as the section head and fellowship director for gynecological pathology at the University of Michigan Hospitals. Dr. Cho received her B.A. from Yale University in 1980 and her medical degree from Vanderbilt University in 1984. She subsequently performed an internship and residency in anatomic pathology at the Johns Hopkins Hospital. From 1988 to 1991, she was a clinical fellow in pathology and a research fellow in cancer genetics, both at Johns Hopkins. She joined the Johns Hopkins University faculty in 1991 as an assistant professor of pathology, oncology, and gynecology and obstetrics, and achieved the rank of associate professor in 1995. Widely recognized as a leading authority in both the basic and clinical study of gynecologic malignancies, Dr. Cho is a prolific investigator with more than 130 peer-reviewed publications. Her work has provided critical insight into the molecular pathogenesis of cervical and ovarian cancer. Dr. Cho is a member of the editorial boards of numerous pathology and cancer-related journals. Her expertise in the field is further shared through her participation in many grant application study sections, review committees, and advisory panels at the national level. Dr. Cho's honors include election to the American Society for Clinical Investigation (2000), the Association of American Physicians (2008), and the National Academy of Medicine (2015).

Heidi Donovan, Ph.D., RN, is an associate professor and director, Office of Community Partnerships, in the School of Nursing at the University of Pittsburgh. Her expertise is in symptom assessment and management for women with ovarian cancer. Her research focuses on developing and testing eHealth interventions to improve patient and caregiver outcomes and on identifying critical components of successful patient education programs. She is the co-developer of the Representational Approach (RA) to patient education, an intervention theory designed to promote behavior change to improve self-management of complex health problems. She has had sustained funding to develop and test a Web-based symptom management intervention (WRITE Symptoms) based on the RA with the aim of improving symptoms, patient–health care provider communication, and quality of life among women with recurrent ovarian cancer. As director of the Office of Community Partnerships in the School of Nursing, Dr. Donovan promotes community engagement by faculty, staff, and students in order to address the health needs of vulnerable, underserved communities in the region. In addition, she has served on the Quality of Life and Ancillary Data Committees of the Gynecologic Oncology Group and serves on the Medical

Advisory Board of the National Ovarian Cancer Coalition. Dr. Donovan has a Ph.D. in nursing from the University of Wisconsin–Madison.

Debra Duquette, M.S., CGC, is the genomics coordinator in the Genomics and Genetic Disorders Section of the Michigan Department of Health and Human Services (MDHHS). She has served as a project manager/director on two Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics cooperative agreements and three CDC Division of Cancer Prevention and Control cooperative agreements with the MDHHS for public health genomics over the past 10 years. Ms. Duquette serves on the Executive Steering Committee for the Patient-Centered Outcomes Research Institute (PCORI)-funded ABOUT Network and provides a leadership role to represent public health. She is also the chair of the Lynch Syndrome Screening Network (LSSN), and the co-chair of the National Academies of Sciences, Engineering, and Medicine Genomics and Population Health Action Collaborative. Ms. Duquette also serves on the Facing Our Risk of Cancer Empowered (FORCE) Advisory Board and the eXamining Relevance of Articles for Young Survivors (XRAYS) Steering Committee. She is a board-certified genetic counselor with more than 12 years of clinical experience counseling more than 8,000 Michigan families.

Robert A. Hiatt, M.D., Ph.D., is professor and chair of the Department of Epidemiology and Biostatistics at the University of California, San Francisco (USCF), and the associate director for Population Science of the UCSF Helen Diller Family Comprehensive Cancer Center. His research interests include cancer epidemiology—especially breast cancer, cancer prevention and screening, health services and outcomes research, social determinants of cancer, and environmental exposures in early development related to cancer. His central focus at UCSF is building a strong interdisciplinary research and training program in epidemiology with a focus on cancer population sciences. He is also an adjunct professor, Division of Epidemiology, University of California, Berkeley, and adjunct investigator at the Division of Research, Kaiser Permanente Medical Care Program in Oakland. From 1998 to early 2003 he was the first deputy director of the Division of Cancer Control and Population Sciences at the National Cancer Institute, where he oversaw cancer research in epidemiology and genetics, surveillance, and health outcomes and the quality of cancer care research. He is a past president of the American College of Epidemiology and the American Society for Preventive Oncology.

Beth Y. Karlan, M.D., is director of the Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, director of the Division of Gynecologic Oncology and the Gilda Radner Hereditary Cancer Pro-

gram, and holds the Board of Governors Chair in gynecologic oncology at Cedars-Sinai Medical Center. Dr. Karlan is also professor of Obstetrics and Gynecology at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA). Her research focuses on the genetic definition and phenotypic determinants of human ovarian carcinomas, molecular biomarker discovery for early detection and prognostication, and inherited cancer susceptibility, and she has been prolific with more than 300 research articles published. She is an American Cancer Society Clinical Research Professor and the editor-in-chief of the journals *Gynecologic Oncology* and *Gynecologic Oncology Reports*. In 2012, Dr. Karlan was appointed by the White House to serve on the National Cancer Advisory Board, and she has testified before the U.S. Congress in support of increased research funding for ovarian cancer. She has worked tirelessly to advance her specialty on behalf of her patients and has served in many professional leadership positions including president of the Society of Gynecologic Oncology, board of directors for the Ovarian Cancer Research Fund and the Conquer Cancer Foundation, and chair of the scientific advisory board of the Clearity Foundation. Dr. Karlan is a magna cum laude graduate of Harvard-Radcliffe College. She earned her medical degree from Harvard Medical School and the Harvard–Massachusetts Institute of Technology Program in Health Sciences and Technology. After finishing her residency at Yale-New Haven Hospital, Dr. Karlan completed a postdoctoral research fellowship in molecular biology at Yale University School of Medicine and a clinical fellowship in gynecologic oncology at the David Geffen School of Medicine at UCLA.

Douglas A. Levine, M.D., is an attending surgeon on the Gynecology Service in the Department of Surgery at Memorial Sloan Kettering Cancer Center, where he also serves as head of the Gynecology Research Laboratory. His laboratory studies novel biomarkers, precision medicine, and rare tumors. Dr. Levine has published more than 150 peer-reviewed articles in addition to several textbooks. He has received the Foundation for Women's Cancer Excellence in Ovarian Cancer Research Prize and the American Congress of Obstetricians and Gynecologists Mentor Award, and serves as the assistant dean of the U.S. Department of Defense Ovarian Cancer Academy. Dr. Levine is the co-chair of the Ovarian Cancer, Endometrial Cancer, and Uterine Carcinosarcoma Working Groups of The Cancer Genome Atlas. He serves as a member of the Scientific Advisory Committee of the Ovarian Cancer Research Fund, the Clearity Foundation, and the Board of The Honorable Tina Brozman Foundation. Dr. Levine is a graduate of Franklin and Marshall College. He earned his medical degree from the Mount Sinai School of Medicine and completed residency at the Mount Sinai Medical Center. He completed clinical and research fellowships at Memorial Sloan

Kettering Cancer Center and is board-certified in obstetrics and gynecology and gynecologic oncology. Dr. Levine has an outstanding level of expertise and leadership in ovarian and endometrial cancer research and a deep commitment to women's health.

Terry Magnuson, Ph.D., was recruited to the University of North Carolina at Chapel Hill (UNC) in 2000 as founding chair of the Department of Genetics and director of the newly established Carolina Center for Genome Sciences. He also created the Cancer Genetics Program in the UNC Lineberger Comprehensive Cancer Center. He was appointed vice dean for research in the School of Medicine in July 2010. Dr. Magnuson is a founding member of the International Mammalian Genome Society. He has served on the board of directors of the Society for Developmental Biology (2000–2006) and the Genetics Society of America (2004–2006). Currently, he is a member of the National Institutes of Health (NIH) stem cell working group (2009–present) and the NIH Council of Councils (2014–present). He was elected to the American Academy of Arts and Sciences (2007), became a fellow of the American Association for the Advancement of Science (AAAS) (2009), and was also elected to the National Academy of Medicine (2012). He is a senior editor for *Genetics* (2009–present), as well as a member of the board of reviewing editors for *Science Signaling* (2010–present). The work in the Magnuson laboratory focuses on the role of mammalian genes in unique epigenetic phenomena such as genomic imprinting, X-chromosome inactivation, and stem cell pluripotency. The laboratory also studies the tumor suppressor role of the BAF/PBAF chromatin remodeling complexes and has developed a novel genome-wide mutagenesis strategy.

Lisa Meier McShane, Ph.D., is chief of the Biostatistics Branch in the Biometric Research Program in the Division of Cancer Treatment and Diagnosis at the National Cancer Institute (NCI), where she advises other programs in the NCI on statistical matters relating to development and use of tumor markers for prognosis, therapy selection, and disease monitoring. She holds a Ph.D. in statistics from Cornell University and is a fellow of the American Statistical Association. Dr. McShane's statistical research interests include biomarker-based clinical trial design, analysis methods for high-dimensional genomic data, multiple comparisons methods, surrogate endpoints, measurement error adjustment methods, laboratory quality control, and biomarker assay analytical performance assessment. Her collaborative cancer research has included gene expression profiling and pathway analysis to predict survival and response to therapy in breast cancer, microRNA profiling of lung cancer, inflammatory and immune profiling of lung cancer, and studies of proliferation markers relevant to breast and colon cancer. She co-led the efforts to develop "Reporting guidelines for tumor marker

prognostic studies (REMARK)" and "Criteria for the use of omics-based predictors in clinical trials." Dr. McShane is co-author of more than 100 publications in statistical and biomedical journals and a co-author of the book *Statistical Design and Analysis of DNA Microarray Investigations*. She is a frequent invited speaker at national and international oncology and statistics meetings. Dr. McShane serves on the Scientific Advisory Board for Science Translational Medicine and is a member of the editorial board for *BioMed Central (BMC) Medicine*. She has been a member of numerous American Society of Clinical Oncology panels and committees, including those which developed guidelines for HER2 and hormone receptor testing in breast cancer, EGFR mutation testing in lung cancer, and use of tumor biomarkers in early-stage breast cancer. Dr. McShane has served on a U.S. Food and Drug Administration/Center for Devices and Radiologic Health Molecular and Clinical Genetics Panel and has been a member of the Institute of Medicine Advisory and Consensus Committees on Management of the Air Force Health Study Data and Specimens.

Kunle Odunsi, M.D., Ph.D., is the cancer center deputy director at Roswell Park Cancer Institute (RPCI), Buffalo, New York. He is also the M. Steven Piver Endowed Professor and Chair of the Department of Gynecologic Oncology, executive director of the Center for Immunotherapy, and co-leader of the Tumor Immunology and Immunotherapy Cancer Center Program at RPCI. He maintains an active, independent laboratory research program that focuses on understanding the mechanisms of immune recognition and tolerance in human ovarian cancer. He is principal investigator of a National Cancer Institute (NCI)-funded Specialized Program of Research Excellence (SPORE) in ovarian cancer, and a multimillion dollar grant from New York State Stem Cell Science Program (NYSTEM) to pioneer a novel strategy of re-programing human hematopoietic stem cells to become a lifelong supply of antitumor immune cells in ovarian cancer patients. He is the co-chair of the NCI Ovarian Cancer Task Force of the Gynecological Cancer Steering Committee. Dr. Odunsi received his Ph.D. in immunogenetics from the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom. He completed his residency in obstetrics and gynecology at the Yale University School of Medicine, New Haven, Connecticut; and sub-specialty fellowship in gynecologic oncology at RPCI. He is a Fellow of the Royal College of Obstetricians and Gynaecologists in the United Kingdom. He is also a Fellow of the American College of Obstetricians and Gynecologists. Dr. Odunsi is licensed by New York State and certified in obstetrics and gynecology by the American Board of Obstetrics and Gynecology. He is also board-certified in the subspecialty of gynecologic oncology. Dr. Odunsi has authored or co-authored more than 250 journal publications and book chapters. He has served on scientific study

sections of the National Institutes of Health/NCI and the U.S. Department of Defense (DoD) Ovarian Cancer Research Program. He serves on the editorial boards of *Gynecologic Oncology*, *BMC Cancer*, *Cancer Immunology Research*, and *Journal for Immunotherapy of Cancer*.

Mary (Dicey) Jackson Scroggins, M.A., is a writer, producer, and founding partner in Pinkie Hugs, LLC (a mother-daughter writing and film production firm specializing in social justice–focused documentaries), and 18-year ovarian cancer survivor and health activist. She co-founded In My Sister's Care, an organization focused on improving gynecologic cancer awareness and care for medically underserved women and on eliminating health disparities. With longstanding relationships throughout the advocacy and research communities, Ms. Scroggins is a member of the board of directors of the Gynecologic Oncology Group (GOG) Foundation and the NRG Oncology Foundation, and a member of the advisory committee for the "Globe-athon to End Women's Cancers," the leadership committee for the MD Anderson Cancer Center's "Women's Cancer Moon Shot Program," the Ovarian Cancer National Alliance's Research Advocacy Committee, and the NCI's Cancer Prevention and Control Central Institutional Review Board. She is also chair of the NRG Patient Advocate Committee, the advocate advisory board of a DoD-funded project focused on the characteristics of long-term ovarian cancer survivors, and the Advocates' Stakeholder Advisory Board of a PCORI-funded program developing a patient-centered aid for treatment decision making, and a co-chair of the Eighth (2015) American Association for Cancer Research (AACR) Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. Previously, she was a member of the NCI's Gynecologic Cancers Progress Review Group and Gynecologic Cancer Steering Committee, a co-chair of its Patient Advocate Steering Committee, a member of the Ovarian Cancer National Alliance Board of Directors, and a peer reviewer and integration panel member for the DoD Ovarian Cancer Research Program. An eclectic writer with a master's degree from Johns Hopkins University, Ms. Scroggins has published essays and articles on topics such as cancer survivorship, health disparities, medical ethics, and fiction on social justice issues. She is also on the editorial board of *Cancer Today*. Her advocacy work is driven by a commitment to medical and health equity.

Anil K. Sood, M.D., is professor and vice chair for translational research in the Department of Gynecologic Oncology & Reproductive Medicine at the University of Texas MD Anderson Cancer Center. He is also director of the multidisciplinary Blanton-Davis Ovarian Cancer Research Program and co-director of the Center for RNA Interference and Non-Coding RNA. His research is focused in three main areas: (1) mechanisms of angiogenesis and

metastasis in ovarian cancer, (2) effects of neuroendocrine stress hormones on ovarian cancer growth and progression, and (3) development of new strategies for systemic in vivo siRNA delivery. Dr. Sood has published more than 450 articles and has authored and co-authored several book chapters, and he serves on the editorial board for several journals. He is a deputy editor for *Gynecologic Oncology*. Dr. Sood has received major recognition for his research accomplishments, including the Hunter Award, the Margaret Greenfield/Carmel Cohen Excellence in Ovarian Cancer Research Prize, and the Gynecologic Cancer Foundation/Claudia Cohen Research Prize for Outstanding Gynecologic Cancer Researcher. He is an elected member of the American Society for Clinical Investigation and an elected fellow of the AAAS.

Shelley S. Tworoger, Ph.D., is an associate professor of medicine and epidemiology at the Harvard Medical School, the Harvard T.H. Chan School of Public Health, and the Brigham and Women's Hospital (BWH). The focus of her research is to enhance ovarian cancer prevention using an integrative and collaborative approach. She heads the ovarian cancer research efforts in the Nurses' Health Studies (NHS/NHSII), is the principal investigator of the Ovarian Cancer Cohort Consortium (OC3), and is the director of the BWH/Harvard Cohorts Biorepository. Her work in ovarian cancer falls into three primary areas: (1) identifying new risk factors, (2) evaluating disease heterogeneity, and (3) elucidating early carcinogenic changes. She is co-author of more than 80 publications on the epidemiology of ovarian cancer. Dr. Tworoger received her Ph.D. in epidemiology from the University of Washington in Seattle.

INSTITUTE OF MEDICINE STAFF BIOGRAPHIES

Tracy A. (Harris) Lustig, D.P.M., M.P.H., is a senior program officer with the IOM. Dr. Lustig was trained in podiatric medicine and surgery and spent several years in private practice. In 1999, she was awarded an AAAS Congressional Fellowship and spent 1 year working in the office of Ron Wyden of the U.S. Senate. Dr. Lustig joined the IOM in 2004 and her most recent work has focused on the health care workforce and the aging of the U.S. population. She has been the study director for several IOM reports, including *Retooling for an Aging America: Building the Health Care Workforce*, *Advancing Oral Health in America*, and *Improving Access to Oral Health Care for Vulnerable and Underserved Populations*. She has also directed workshops on the allied health workforce, telehealth, assistive technologies, hearing loss, and home health care. She co-directs the Forum on Aging, Disability, and Independence. Dr. Lustig has a doctor of podiatric medicine degree from Temple University and a master of public health

degree with a concentration in health policy from The George Washington University.

Mark D. Stewart, Ph.D., is a research associate with the IOM. He received his Ph.D. from the University of Alabama at Birmingham. During Dr. Stewart's graduate work, he investigated the role of the tumor microenvironment in cancer progression and metastasis. He was a recipient of several awards, including the Ruth L. Kirschstein National Research Service Award Predoctoral Fellowship from the NCI. His work has been published in several peer-reviewed research and review articles. In addition, he has authored several editorial pieces for *ASBMB Today*, the newsletter for the American Society for Biochemistry and Molecular Biology. Aside from his work at the IOM, he is actively engaged in developing professional advancement sessions and resources for early career scientists in his role as the chair of the Associate Member Council of the AACR.

Sapana R. Vora, Ph.D., trained as a cancer biologist and has a passion for science, politics, and the myriad ways in which they intersect. Dr. Vora earned her Ph.D. at the University of Chicago, where her dissertation delved into inherited risk genetics for acute leukemia. Prior to graduate school, she double majored in biology and English at the University of North Carolina at Chapel Hill, where she volunteered as a laboratory assistant, was involved in a science advocacy group, and interned at GlaxoSmithKline. She was a 2015 Christine Mirzayan Science and Technology Policy Graduate Fellow and research associate at the National Academies of Sciences, Engineering, and Medicine. In September 2015, Dr. Vora started her AAAS Science and Technology Policy Fellowship working on biosecurity at the U.S. Department of State.

Noa L. Nir is a senior program assistant with the IOM, currently serving on the Board on Health Care Services and the Food and Nutrition Board. Prior to joining the IOM in 2014, Ms. Nir acted as the youth director for Temple Rodef Shalom in Falls Church, Virginia. She earned her bachelor's degree in English with a concentration in creative writing from the College of William and Mary in Williamsburg, Virginia, graduating magna cum laude in December 2013. Ms. Nir has also held several internships with organizations such as Just Vision, the Embassy of Israel, and the American Task Force on Palestine. Ms. Nir writes and teaches a creative writing workshop to young writers in her spare time, and her poetry has been published in numerous publications. She won the Academy of American Poets' Prize for a Single Poem in spring 2013.

Sharyl J. Nass, Ph.D., is director of the Board on Health Care Services and director of the National Cancer Policy Forum at the National Academies of Sciences, Engineering, and Medicine. The work of the Board is helping to shape the direction of health care in the United States and abroad. The Board considers the entire health care system in order to ensure the best possible care for all patients. Its activities pertain to the organization, financing, effectiveness, workforce, and delivery of health care. The Cancer Forum examines policy issues pertaining to the entire continuum of cancer research and care. For more than 15 years, Dr. Nass has worked on a broad range of health policy topics that includes the quality of care, clinical trials, oversight of health research, developing biomarkers and omics-based tests to guide patient care, technologies and quality standards for breast imaging, strategies for large-scale biomedical science, and contraceptive research and development. With a Ph.D. in cell and tumor biology from Georgetown University and postdoctoral training at the Johns Hopkins University School of Medicine, she has published papers on the cell and molecular biology of breast cancer. She also holds a B.S. in genetics and an M.S. in endocrinology and reproductive physiology, both from the University of Wisconsin–Madison. In addition, she studied developmental genetics and molecular biology at the Max Planck Institute in Germany under a fellowship from the Heinrich Hertz-Stiftung Foundation. She was the 2007 recipient of the Cecil Award for Excellence in Health Policy Research, the 2010 recipient of a Distinguished Service Award from the Academies, and the 2012 recipient of the IOM staff team achievement award (as the team leader).