Cancer-Related Genetic Testing and Counseling: Workshop Proceedings

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CANCER-RELATED GENETIC TESTING AND COUNSELING

Workshop Proceedings

National Cancer Policy Forum

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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Contents

Abbreviations and Acronyms

AAFP	American Academy of Family Practitioners
ACMG	American College of Medical Genetics
ACS	American Cancer Society
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
ASCO	American Society of Clinical Oncology
ASHG	American Society of Human Genetics
ASR	analyte-specific reagent
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments of 1988, or CLIA
CME	continuing medical education
CMS	Centers for Medicare and Medicaid Services
CPT	current procedural terminology
DHHS	Department of Health and Human Services
DOE	Department of Energy
DTC	direct-to-consumer
ELSI	ethical, legal, and social implications
FAP	familial adenomatous polyposis

FDA	Food and Drug Administration
FTC	Federal Trade Commission
FTE	full-time equivalent
GAO	Government Accountability Office
GI	gastrointestinal
GINA	Genetic Information Nondiscrimination Act
GNRH	gonadotrophin-releasing hormone
GRE	Graduate Record Examination
HIPAA	Health Insurance Portability and Accountability Act
HMO	health maintenance organization
HNPCC	hereditary nonpolyposis colorectal cancer
HRSA	Health Resources and Services Administration
IOM	Institute of Medicine
IRB	institutional review board
IVDMIA	in vitro diagnostic multivariate index assay
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NPI	national provider identification
NSABP B-04	National Surgical Adjuvant Breast and Bowel Project
NSGC	National Society of Genetic Counselors
OCN	oncology-certified nurse
PSA	prostate specific antigen
RBRVS	resource-based relative value system
RVU	relative value unit
UPIN	universal provider identification number
USC	University of Southern California
USPSTF	U.S. Preventive Services Task Force

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Introduction

These proceedings of a workshop presented to the Institute of Medicine's (IOM) National Cancer Policy Forum (the forum) on March 30, 2007, are the result of forum discussions about genetic testing and counseling at its meetings on June 16 and October 30, 2006. Those discussions, led by forum members Betty Ferrell and Patricia Ganz, noted 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. Drs. Ferrell and Ganz proposed that the forum could provide a useful review of the various important implications of these issues by holding and reporting a workshop on the subject. They volunteered to work with staff to organize and lead such a workshop. The agenda for the workshop is reproduced in the appendix to these proceedings. Chapter 2 includes the presentations of the invited speakers and the comments of speakers, forum members, and others in attendance as transcribed and edited to eliminate redundancies, grammatical errors, and otherwise make them more readable. Material from PowerPoint presentations has been added to the text to clarify the speakers' messages as needed.

This workshop consumed the major part of a regularly scheduled meeting of the forum. The forum was established as a unit of the IOM on May 1, 2005, with support from the following agencies of the U.S. Depart-

ment of Health and Human Services (DHHS): the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and the Health Resources and Services Administration (HRSA); as well as from the following private-sector organizations: the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO), C-Change, and (for the first year only) UnitedHealth Group. The forum is a successor to the IOM and National Research Council's (NRC's) National Cancer Policy Board (1997–2005) and was designed to provide its 21 governmental, industry, and academic members a venue for exchanging information and presenting individual views on emerging policy issues in the nation's effort to combat cancer. Publication of these proceedings informs the forum and, in addition, provides an opportunity to make the information and views presented and discussed at the workshop available to a wider public audience. Only what was actually communicated at the workshop is reported here without additional comment, interpretation, or analysis, although these proceedings might serve as an opening to additional IOM study at some future time.

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Prepared Presentations and Discussion

Dr. Patricia Ganz, Professor of Medicine, UCLA: The Promise and Pitfalls of Cancer-Related Genetic Counseling and Testing: I am going to give an overview to explain why we brought up cancer-related genetic testing and counseling as an issue. We have had clinical genetic testing for the BRCA-1 and -2 breast cancer genes for about 10 years. As we end this decade, we feel we have passed an important milestone, and we should think about what has happened over this time. In addition, legislation against genetic discrimination has been on the agenda in Congress for probably 10 or 11 years and has finally been approved in the House of Representatives with hope of passage this year. So I think there are a number of issues that make it timely for us to begin a discussion.

In setting the stage for today's speakers, I will be somewhat anecdotal and provide examples that I hope illustrate why we are here today. As a historical overview and dynamic case study of how we got to our present situation, I will start with what I think has been the successful integration of genetic testing and counseling in the management of breast cancer. I will try to fit clinical cancer genetics into the prevention paradigm, discuss some access and direct-to-consumer marketing issues, and sum up with some of the challenges that I see, hoping that our speakers today will cover them in greater detail.

I started my medical school surgical rotation in 1971 which brought me to part of the breast service and a surgeon at the county hospital who was participating in a National Surgical Adjuvant Breast and Bowel Project

(NSABP B-04) clinical trial that was comparing radical mastectomy to modified radical mastectomy. To my surprise, a woman at that time had to consent to either a radical or modified radical mastectomy before she even knew she had cancer. A frozen section diagnosis of her breast mass was made while she was on the operating table, and if she had cancer she would either have the standard radical procedure or the modified radical mastectomy. She awoke from anesthesia not knowing if she had breast cancer and whether she had the very radical or less radical procedure. This trial was important in showing that radical mastectomy was no better than modified radical mastectomy, and fortunately we have advanced in the local treatment of breast cancer since that time.

Today, most breast cancers are discovered through mammography, and more than 50 percent of them are stage I small tumors. In the early 1980s, advocates suggested that a two-step procedure was needed to provide a diagnosis and an opportunity to consider treatment options before surgery. As a result we now do small incisional biopsies or lumpectomies, sentinel node biopsies, and breast irradiation in many instances. We also have trials going on to examine whole versus partial breast radiation for women with lumpectomies, because long-term survivors may develop a second cancer in the same breast, and if they have already experienced all the radiation they can tolerate in that breast, mastectomy will be their only treatment option at that point.

Clinical genetic testing for breast cancer genes is often done prior to surgical decision making. If a woman is going to need hormonal therapy or chemotherapy before her definitive surgery, genetic testing may weigh very heavily in whether she decides to have a mastectomy on the tumor side or even bilateral mastectomy as part of the initial treatment planning. Because endocrine therapy may be given for up to 10 years for primary or secondary prevention, genetic information may have substantial implications. We recognized that breast cancer is a systemic disease, and through clinical trials and evolving practice, we have achieved important decreases in incidence and improvements in survival. We have eliminated the one-step surgical approach and turned to minimally invasive biopsies, lumpectomies, and radiation, with mounting evidence for as good or better results with less radical options.

The bottom line here is increasing patient involvement in surgical decision making and also now genetic decision making, although what I am describing in terms of the incorporation of genetic testing and decision making as part of treatment management may only be occurring at tertiary

centers—not yet the norm, but the way things are developing. We have important improvements in survival as a result of our progress: 90 percent 5-year survival rate for early stage patients, more than two million breast cancer survivors alive today, and continued improvements expected. These data have important implications: if we expect women to live a long time, having as much information about their potential risks for a second cancer either in the breast or the ovaries or some other organ is critical to decision making and treatment planning.

Important discoveries in the 1990s improved our understanding of risk factors for breast cancer. Two genes, BRCA-1 and -2, thought to be responsible for 5 to 10 percent of breast cancers, were discovered on chromosomes 17 and 13, respectively. They could be responsible for as many as 20,000 of the 200,000 breast cancers diagnosed each year in the United States; these 20,000 women might benefit from genetic information to assist decision making at diagnosis. Certainly after diagnosis in terms of the prevalent cases, there are many women who may be carrying genetic predisposition genes that would affect their future health as well as that of the families, so the potential ramifications of genetic information are important.

What happened at UCLA as an exemplar of progress at the end of the twentieth century? We were involved in the first breast cancer prevention trial, and shortly after that I established a high-risk program within our Revlon/UCLA breast center. It became clear to me that other centers around the country that were doing the leading-edge work in terms of the alpha and beta testing for genetic testing were beginning to see these high-risk populations and that this would be an important clinical service as well as an avenue to do clinical translational research. When clinical testing became available in 1997 for the BRCA-1 and -2 genes, we had a decision to make: were we going to put this into the clinical testing arena with all of the other genetic testing that was done with prenatal and other conditions, or were we going to somehow treat this differently? Because of concerns about the potential for genetic discrimination, the time needed to counsel women or others, we believed it best to proceed through a research protocol, not only to provide these services to people in a situation where they could be protected against potential legal or discriminatory practices, but also to collect research data on outcomes.

We started this as the UCLA Family Cancer Registry and Genetic Evaluation Program, a shared resource at the cancer center. We opened this up to anyone who had a cancer history, so it wasn't just breast and ovarian cancer. Patients who enter this program are not necessarily seen just once,

but may be seen repeatedly and benefit as new science provides new information on their condition and leads to new decision making.

A woman came to us in 1996 for high-risk surveillance in the course of clinical assessment and evaluation. Her sister had bilateral breast cancer diagnosed at age 35, and her mother had breast cancer diagnosed at age 45 and died at age 48 with metastases. Annual screening mammography and clinical breast exams three to four times a year were recommended. In 1999 she joined the family registry. In November of 2000, her mammogram was negative, but early in 2001, at age 41, she was diagnosed with breast cancer. As she was going through her surgical decision making, she considered whether she should have bilateral mastectomies. Because of her strong family history, we did genetic testing, and she had no evidence of a deleterious breast cancer gene mutation. We also pursued this further by testing for the tumor suppressor gene, PTEN, because of her very strong family history. When this turned out to be negative, she decided just to have a lumpectomy and radiation therapy because no genetic predisposition could be found in spite of three first-degree relatives with breast cancer, one of them bilateral.

Subsequently, we learned of new mutations (large deletions) in BRCA-1 that were associated with the risk of breast cancer in similar families, and on retesting she was found to have one of these very large deletions that was the cause of what was going on in her family. She then elected to have bilateral prophylactic mastectomies and also bilateral oophorectomies because of the very strong risk of both of these diseases. The 2002 update of her pedigree at this point in time is displayed in Figure 2-1 with a summary of the relevant events. The patient is indicated in this pedigree by the large arrow.

We fortunately have had the ability to perform long-term tracking of the people in our registry. We send them an annual questionnaire. I have had very good genetic counselors who work with me and who remember these cases. We probably have many more of them in our registry with family histories and unknown mutations. This is the luxury of having a research registry, but the average patient who has his or her blood drawn by a medical oncologist or even a clinical genetics counselor may not have such a luxury. The patient may not be well enough informed to follow through in this evolving field, where new information is coming continually. This is going to be a long-term problem.

Ellen Stovall, CEO, National Coalition for Cancer Survivorship: Are you still following this woman, and if so, how is she doing?

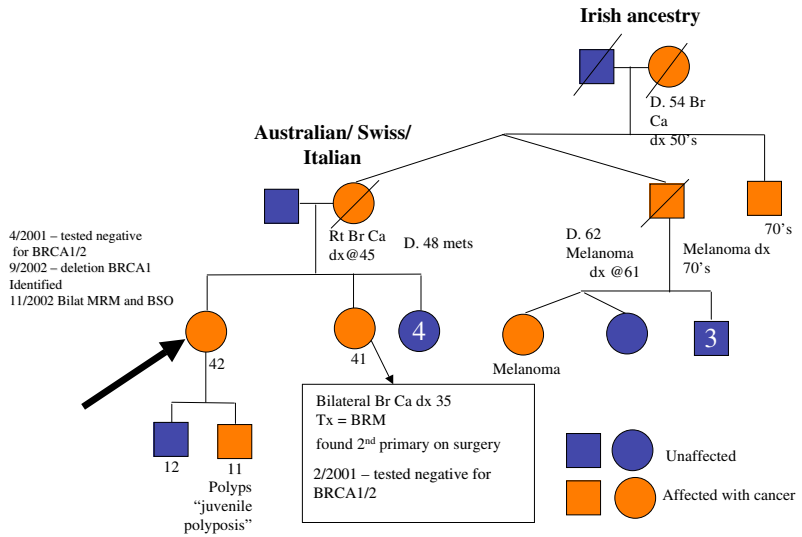

FIGURE 2-1 Pedigree of a high-risk patient.

Dr. Ganz: Yes, we are. She is doing very well, and she is a very outspoken advocate for this kind of testing and follow-up.

I have shown you a nice example of how this can work and work well. But I don't think this is the routine around the country. I think my colleagues today who are going to be discussing this will tell us about what is going on in the real world. If you think about where clinical cancer genetics belongs, it is in the prevention paradigm: either primary or secondary prevention. In somebody who doesn't have cancer yet, we want to prevent cancer in the future. If somebody, genetically predisposed or not, has already had cancer and is, therefore, at highest risk for a second cancer, we want to intervene there too. Survivors account for about 15 percent of all new cancer diagnoses that occur every year. It takes a very long period of time for breast cancer to develop from the very first cell that is malignant to one that we can detect—dissemination occurs in the interval between the first cancer cells and cancer detection. We know that hereditary cancers account for about 5 to 10 percent of all cancers. If we can find people with the first hereditary mutation who then are going to acquire other mutations that will lead to cancer, we have a real opportunity to intervene.

How do we find who is at risk for breast, colon, or prostate cancer, or melanoma and other diseases where we either have those genes identified or will in the future, when there are so few individuals? I think this is the real challenge that we face from the prevention and population perspective. Characteristically, in families with sporadic breast cancer, none of the cancer is diagnosed prior to age 60, there is no ovarian cancer, and no clear pattern on one side of the family or the other. Characteristically, in hereditary breast cancer, onset of cancer is under age 50, ovarian cancer (though not always present) occurs at any age, breast and ovarian cancer occurs in the same individual, there is male breast cancer, and there is Ashkenazi ancestry. We know that one in 40 to one in 50 individuals of Ashkenazi heritage are likely to carry one of the three founder mutations for breast cancer. The American Society of Clinical Oncology's (ASCO's) most recent guidelines for breast cancer care and surveillance recommend that any younger woman of Ashkenazi Jewish heritage with breast cancer, even if there is no family history, should have genetic testing.

So the key is the family history on both sides of the family, maternal and paternal, to accurately assess risk and make decisions about whether it is appropriate to do testing and genetic counseling. From the speakers today, we will hear who in the workforce should be doing that genetic counseling, whether we have enough people in the workforce, and whether we can rely on primary care physicians to take the appropriate family histories. Genetic testing just gives you information; it doesn't tell you what to do. We need the expertise of someone who knows about the genetics and the risks for various cancers and what the preventive strategies might be. We should suspect hereditary cancer when there are two or more relatives on the same side of the family, an early age at diagnosis, multiple primary tumors, bilateral or rare cancers, a constellation of tumors consistent with a specific cancer syndrome (e.g., breast and ovarian cancer, colon and uterine cancer, colorectal cancer associated with polyposis), autosomal dominant transmission, and the Ashkenazi heritage in particular.

Increasingly there are reports of multiple cancers associated with hereditary predisposition genes. Genetic testing of incident cases of ovarian cancer in the population identified high rates of BRCA-1 and -2 expression, and complete pedigrees found that the women who were gene carriers had many other family relatives with a constellation of other common solid tumors—a different way of case finding. This finding needs to be corroborated, but we know already about the breast-ovarian association or the association between BRCA-2 and pancreatic and possibly prostate

cancer and melanoma, or BRCA-1 and possibly testicular and some gastrointestinal (GI) cancers.

Dr. Harold Moses, Director Emeritus, Vanderbilt-Ingram Cancer Center: What proportion of pancreatic cancer patients have BRCA-2?

Dr. Ganz: It is about 5 to 10 percent, so it accounts for a lot of the familial pancreatic cancers. We have now a funded screening study to go back to our registry and identify BRCA-2 carriers with pancreatic cancer in the family. I think this is the tip of the iceberg in what we understand. I think as clinical genetic testing becomes more widespread for cancer predisposition and people recognize this, we are going to become more aware of other sites. Because most of us do not routinely take a thorough family history of our cancer patients, we don't consider or discover family connections. But I think as research evolves we are going to see predispositions in other organs.

You have heard already about the success in tertiary centers of the integration of breast and ovarian cancer, genetic testing, and screening. This has likely occurred because we have had people who have been interested from the research standpoint, but also there is a high level of consumer awareness and a lot of available breast cancer information, and physicians who are treating these patients are aware that this is an issue particularly in the young patients who present to them.

We have a diametrically different experience with colorectal cancer patients. It has been very difficult to get the attention of gastroenterologists. There are many published papers describing that people who have family histories of colorectal cancer are not coming in for genetic testing. Clearly, a colon full of adenomatous polyps in familial adenomatous polyposis (FAP) is a signal, and those patients will be referred for testing. However, in attenuated FAP, there may not be as many polyps in the colon, so it requires an astute gastroenterologist to take a history and refer. There are new mutations, spontaneous mutations where the family history may not be as strong.

There has not been as much patient demand from the colorectal cancer community. We are talking about a community that perhaps is not as active as the breast cancer community in advocacy. There is also the thought that the family members will be screened with colonoscopy. If your mother has colon cancer at age 40, it is agreed that her children need to be screened, but half of them might be screened intensively unnecessarily because they don't carry a mutation. Similarly, her children would begin screening at a

younger age, but half of them might not need that. It would be desirable to avoid overscreening in terms of cost and psychological morbidity, so valuable decision making could be facilitated if genetic testing was done. This lack of patient and doctor awareness and utilization, and even less frequent follow through after referral, bespeaks a different culture, although I think that this is beginning to change and that gastroenterologists and GI oncologists now have begun to see the importance of testing to some extent because there are associated cancers.

Mutations involved in the development of hereditary colorectal cancer include FAP and hereditary nonpolyposis colorectal cancer (HNPCC). Testing is more complicated for this cancer, and it is much more difficult for medical oncologists or general physicians to do in their practices, whereas the BRCA-1 and -2 mutation testing and preventive strategy are much more straightforward. The very high risks of lifetime development of colorectal cancer, 78 percent, or endometrial cancer, 43 percent, and other cancers in HNPCC mutation carriers suggest preventive interventions, such as prophylactic hysterectomy in female carriers or upper endoscopic examinations to screen for stomach cancer (19 percent) (Aarnio et al., 1995).

With HNPCC we see a wide variety of cancers, and I think we are probably going to see more of that with the breast cancer genes as well, because these mutations are in every cell of the body, so the potential to develop a malignancy is widespread. As in breast cancer, surveillance is valuable in HNPCC families too, reducing the incidence of cancer from 11.9 percent to 4.5 percent in one study (Jarvinen et al., 1995). Breast and colorectal cancer are two major diseases that are very common in the population. We know that 5 to 10 percent of the individuals who are getting these diagnoses were predisposed. Could we have prevented the disease, could we have made it possible for these individuals to never have developed cancer? That is why I see this as an important prevention paradigm.

Now, in addition to the barriers that I have discussed, are there others that might limit our access to quality genetic testing and counseling? There are some important structural problems as my colleagues who are speaking today will report in more detail. Physicians do a poor job of taking a family history. The surgeon general and the CDC have had campaigns on this, and there is increasing awareness. And family histories need to be refreshed over time to include disease events (such as cancer) occurring after the original history was taken.

There are a limited number of trained genetic counselors, and I think we are going to hear about that. I don't know what the exact number is, but

it is about 500 to 600 in the cancer genetic interest group of the National Society of Genetic Counselors, according to Dr. Weitzel. This kind of counseling is complex and takes time. Even with the more straightforward tests such as BRCA-1 and -2, there are variants of uncertain significance. This means these variants are polymorphisms that might lead to a deleterious mutation and a risk of getting cancer or later might be determined nonharmful—it is uncertain. It is a tracking issue. When tests are ordered by an oncologist or another physician and a variant of unknown significance is found, the patient may be told that the physician cannot interpret the result. These patients may wind up coming to us, and we have to try to explain it to them. So we need to prepare the patient before we even do the test that this could happen—that we might have an inconclusive finding. For colon cancer tests, it may be much more complicated to strategize. The truth is, we have a limited number of clinical tests available, so this is not something we would be asking all doctors to do in their offices, because it is quite complex.

Direct-to-consumer marketing exists over the Internet. Genetic counselors being in short supply, a patient or consumer can get specific educational information from websites without risking genetic information in his or her medical record. Counseling sessions can occur over the phone with a counselor from a particular company. Arrangements to draw blood and send it to the standard laboratory can be made, and results returned to the patient or consumer. This has the advantage of being available, convenient, and private. But in terms of quality control, are we dealing with the worried well person here, who is deciding to have these tests on his or her own, or is it providing a service to people who may not have access? Other ways of delivering the service have been funded by the National Human Genome Research Institute's Ethical, Legal, and Social Implications (ELSI) program using conferencing by telephone, counseling and other tests, video conferencing, group counseling, and other strategies.

Limited health insurance coverage for counseling and testing is another barrier. I have not experienced this in my urban area, but I hear about it at other places such as the M.D. Anderson Cancer Center. Patients are referred and then they find out that either they don't have insurance coverage for the genetic test or the copayment is 50 percent— it could be for both the counseling and the testing—for a test that costs over $3,000. Unless patients truly understand that this is important to their care, they may choose not to have the test. We will have other people talking about health insurance and employment discrimination, issues that are of concern for everyone.

Concern about employment discrimination is one of the reasons that at UCLA we had separated our testing into research protocols. Nevertheless, we are now moving into the clinical arena as many of our patients end up having preventive surgery, and information about their genetic tests gets into the record as part of that clinical intervention, or in the case of women with breast cancer who are going to need magnetic resonance imaging (MRI) screening, genetic information is needed in the record to justify the special imaging. I think there is a trend, and the recent genetic discrimination legislation will address this.

One of the other hidden messages is that there is inadequate reimbursement for health-care providers to perform counseling and testing. Even though there is reimbursement for an initial consultation visit, many additional hours can be spent discussing and supporting these patients as they go through their decision making. It is very complex and labor intensive for counselors and physicians. Even though it is just a blood test sent to the laboratory, we have to identify the potentially at-risk population, do pretest counseling, obtain informed consent for the test, decide on the right tests to do, disclose and explain the results (separately after 3 to 4 weeks waiting for the laboratory report), and then make sure that the patients know what to do with the test information and what their options are. This process relies on shared decision making and a very intense interaction with the patient or healthy person.

We can experience with patients a range of emotional responses, particularly if they are not prepared for a positive result. If the doctor has warned there is a high likelihood and the patient finds out that they are indeed positive, that is fine, but if counseling has implied that testing is being done just to be safe, and the patient does not expect the abnormal result, it can be very difficult. We have found that patients with cancer already, the breast cancer patients in particular, who might be expected to value an explanation for their disease, are sometimes more distressed because they know what cancer means, and they now have to think about it again, make decisions about preventive treatment, and consider informing other family members, those who are at risk. Very often when that information suddenly and unexpectedly involves the man's side of the family, where there has been no expression of the disease, it can be very challenging.

There is a website for women who have had breast cancer in their family called FORCE (Facing Our Risk of Cancer Empowered); it is like many other patient advocacy awareness and educational resources that are available. I thought it was interesting that they referred to themselves as "pre-vivors."

Cancer pre-vivors are individuals who are survivors of a predisposition to cancer but have not developed the disease; they are those who are living at risk. I don't know that we should be making patients out of healthy people, but it is an interesting example of some of the current thinking.

I am very excited about the speakers we have here today, because we are focusing on forum initiatives to identify and define the challenges of delivering quality care to those who have cancer, are survivors (and many of those will have had a hereditary predisposition to cancer), and then the large number of pre-vivors who will benefit from high-quality and affordable genetic counseling and testing without the fear of discrimination.

Dr. Margaret Spitz, Chair, Epidemiology, M.D. Anderson Cancer Center: That was a wonderful overview, Dr. Ganz. Could you briefly say what your thoughts are about the American Cancer Society (ACS) recommendations for breast MRI in high-risk women?

Dr. Ganz: I got a preview of the recommendations last week, so I have been going back and forth e-mailing my genetic counselors all this week. The ACS in its enthusiasm for screening can often push to the edge of the evidence. This doesn't mean it is either right or wrong. I was talking to a breast surgeon the other day, and he was saying maybe 20 percent of his patients with breast cancer now get an MRI in their diagnostic workup. He sees perhaps 350 new cases a year. So now if he needs to have an MRI on the contralateral breast in every woman he diagnoses, he fears that there will not be sufficient MRI services available. Women who have had one breast cancer already are clearly at high risk for another.

There is also a concern about the quality of MRI services. A very good tertiary center with experienced imagers such as ours will not accept the films from an outside community. The quality is often poor, and there is an issue with liability in terms of interpretation. So I am not sure that we have the infrastructure to do all these MRIs. Also, we did a rough calculation, and the 20 percent lifetime risk (that would be somebody with one first-degree relative of any age and say a biopsy) adds up to a lot of people to be screened. We definitely have been screening our carriers with MRI, and we have patients already asking for MRI. Perhaps Dr. Niederhuber from the NCI will weigh in on this at some point, but I think it is an issue.

Dr. John Niederhuber, Director, National Cancer Institute: In my experience as a surgeon, MRI has been very helpful to me many times in trying

to sort out the difficult patient. I was just thinking as you were talking of a call I had a few weeks ago about a patient whose mammogram showed a potential second site. We sent that patient to a good center, which, as you say, is very important. She ended up with multiple lesions in the involved breast and a contralateral lesion as well, and she went the route of a bilateral mastectomy instead of the original plan of a simple lumpectomy and rather inadequate treatment. So MRI is certainly the state of the art, although how we are going to implement it; how we are going to afford it; and how we are going to educate, train, and build up the workforce to do it are real questions.

Dr. Ralph Coates, Associate Director for Science, Centers for Disease Control and Prevention: I was curious whether your criteria for identifying high-risk women in terms of family history are different from those that are given by the U.S. Preventive Services Task Force (USPSTF) in their recommendation for BRCA genes. They don't recommend surveillance. I think they recommend testing and then potentially counseling for surgery.

Dr. Ganz: The USPSTF may not have reviewed this in the last few years. Dr. Weitzel might want to talk about this as well. The Toronto group and also the European groups that have been doing cohort evaluations in the gene carriers have found much higher detection rates of second cancers or new cancers in gene carriers who have had MRI, ultrasound, breast exam, and mammography simultaneously (Warner et al., 2004). So you detect the cancers better. These are not randomized trials, they are prospective cohort studies. Mammograms are not very sensitive in young women with dense breasts. For these very high-risk women, who have had multiple relatives with breast cancer in their twenties and thirties, we don't want them uniformly to have preventive mastectomies. I am not an advocate of that by and large, although obviously I will support a patient's decision. But early detection can lead to very good outcomes for these women.

Dr. Niederhuber: There are some patients who have had multiple needle biopsies and are frequently requested to have 6-month follow-ups. Those patients obviously are outstanding candidates for enhanced MRI. I was thinking as you provided this wonderful review of the complexity of where we are headed, that we are only today scratching the surface. In only a few years we are going to have to wrestle as a community with whole genome sequencing and what to do with all that information, and which patients will

participate or choose not to participate. Then there is the drug development area, where we are also going to be applying genetics and pharmacogenetics to therapy decisions: who will respond to this drug, in this way, who will have this set of toxicities? All of that highly personalized information we can glean from an understanding of the genome of the individual patient. So the complexity of treatment decisions and the policies that we are going to need to manage such information, in addition to the informatics and analytical workforce, will be a real challenge for my colleague from CMS.

Dr. Barry Straube, Chief Medial Officer, Centers for Medicare and Medicaid Services: It is already hitting us, and interestingly it is the BRCA markers right now. We had an instance where one of the local carriers was denying coverage for reconstructive surgery in a woman who had had bilateral mastectomies and bilateral oophorectomies. The rationale was that the screening for BRCA genes wasn't a covered benefit under Medicare, which is true, but has nothing to do with whether the surgery should have been covered or not. But it forces the issue of some debate internally; can we cover BRCA testing, let alone all the other testing that is going to face us very soon?

Dr. Ganz: I think CMS does cover BRCA testing.

Dr. Straube: Yes, but it is not by a national coverage decision. So, this is causing a discussion where local carriers may have made a decision to cover it. Yet, when you examine the law, there is the question of whether it is a screening test, a diagnostic test, or a biomarker that you can call therapy—all these kinds of questions. Let me assure you, it is not resolved. Regardless of how it comes out, it opens up a Pandora's box for a whole series of other questions. I think you did a very nice job too on the counseling aspect, Dr. Ganz. Do we have enough people? No. The people that we have or will have, are they adequately trained? How do you accredit those services, and how do we pay for those services? These are important questions.

Dr. Ganz: Dr. Weitzel and I are neighbors, and we cover the same region and population. But there are many managed care groups in our area that want to provide this service to their patients, and they refer them all to us, because a medical group, even though it may have 400,000 or 500,000 covered lives and is offering an extensive array of medical services, will not have the expertise. So we have been getting referrals from many of them. If we or

City of Hope didn't exist as special places to provide these services, I doubt they would be provided. Most of our services are covered by philanthropic funds, not reimbursement, and this is the problem in terms of how we are going to provide quality care.

Dr. Jeffrey Weitzel, Director, Department of Clinical Cancer Genetics, City of Hope Cancer Center: My comment goes back to the MRI issue. There is no debate in my mind about the highest-risk individuals, because they are balancing mastectomy versus competence in effective screening. With a combination of mammogram and MRI being 95 percent sensitive, and the Warner study results referred to earlier, we are at the level where I can start counseling my patients based on a good negative predictive value of testing which is really critical. But I agree entirely that at the 20 percent risk level, it really becomes much more challenging to justify.

Dr. David Parkinson, Senior Vice President, Oncology Research and Development, Biogen IDEC: Just to pick up on Dr. Niederhuber's point, this kind of information in the history will become increasingly important as we move therapeutics earlier. You can call it what you want, call it chemoprevention if you want. The histories and the biological characterization may very well determine differences in the approach to therapy. These are probably biologically different kinds of tumors in the different settings. To the extent that we can recognize this, we can develop therapeutic strategies to prevent or to treat early more successfully.

Dr. Ganz: We have been getting women referred to us who have triple negative breast tumors—estrogen and progesterone receptor negative and HER2/neu negative. We know that is common in the African-American population, and we don't know if the BRCA-1 gene is methylated in African-American women, and that is why they are getting that expression. These women do not have much of a family history, but because of the characteristics of the tumor and their relatively younger age, we wonder if they could have a BRCA-1 tumor, because this picture is characteristic of that tumor. We have had several of them now who have tested positive, where the family history was not that salient, but the biological characteristics of the tumor, the fingerprint of the tumor, pointed to BRCA-1.

Dr. Parkinson: And we have therapeutic approaches emerging that can actually alter that situation.

Robin Bennett, Senior Genetic Counselor, Assistant Director Cancer Genetics, Medical Genetics Clinics, University of Washington Medical Center: Current and Future Demand for Cancer-related Genetic Counseling and Testing Services: Those who come to us for genetic counseling have a lot of questions. Am I going to be discriminated against? Will my family be insurable? Do I want to know this information, and how will it affect my family? What can be done to prevent cancer? If I test negative will I still get cancer? Genetic consultation offers new objective and scientific knowledge from outside the person, but it arouses within the person old, subjective, and irrational knowledge of personal grief, angers, and confusions about the connections between family and illness (Lehmann, 1997). So these tests are not just yes-no answers. There is a lot of counseling that goes with them.

The goals of cancer genetic counseling and testing are many, but some of the major ones are: at what age should we begin screening, should we be screening some people younger than average, should some have more intensive screening as we have discussed with breast MRIs or colonoscopies as compared to flexible sigmoidoscopy, are there healthy lifestyle choices that we can be offering, and is there chemoprevention such as tamoxifen or other agents that could help prevent cancer in the first place? Finally, of course, can we provide counseling to promote informed choices and adaptation to the condition.

Who is providing these services? Many people may, not just genetic counselors. There are many factors that may contribute to who will be providing services. These include competency, education, and training, regulations, state license and practice acts, local organizations and market conditions, supply and demand, reimbursement, local collaborations, and political strength and vision of the profession.

The local market varies around the country. There may be historical groups that have provided counseling services or oncology services that people in the health professions are turning to. Varying supply and demand, not only related to the health professional who may be referring the patient, but also the patient groups themselves, are important. If there is an advocacy group that is pushing for BRCA-1 or -2 testing in your community, those services may be more readily available than in some other communities. Organizational structure is important; some health maintenance organizations (HMOs) have a whole network with policies on who is referred and to whom they are referred. Geography makes a difference. I know in my region in the Pacific Northwest, there are many geographical barriers to services.

We have much better health services in general in the northwestern part of our state than in eastern Washington, and the insurance levels and access to qualified health professionals are different.

Coverage for reimbursement varies. There are disparities in service receipt with white, well-insured individuals being favored. These services are important to well-educated people who can understand the concepts in the first place, and that counseling has value to them. The strength of the health professions in advocating that their members should be providing the services also makes a difference.

Today, I will talk about my own experience as a genetic counselor at the University of Washington since 1984. I will provide information about the training of genetic counselors, the training programs, and the demographics of the people providing these services, and then make some recommendations for expanding the genetic counseling workforce. This information is based on a report I gave to the Secretary's Advisory Committee on Genetic Health in Society in my role as President of the National Society of Genetic Counselors in 2003.

The experience of our medical genetics clinic is probably similar to that of other genetics clinics around the country. Our caseload has expanded from about 300 patients per year in 1996 to almost 1,400 in 2006. We are not a pediatric clinic; we see primarily adults, and the demand for our services has expanded in large part as we have been able to offer genetic testing to patients. In 1993 when Huntington's disease testing first became available, our neurogenetics clinic was concerned, because 90 percent of at-risk people said that they wanted to have this test. However, it ended up that maybe 20 to 30 percent of those actually had the testing, so they have not overwhelmed our clinic. At that time, no one talked about cancer genetics. But as testing became available, our clinic has met the demand, to the point that now almost half of our patients are cancer genetics clients, almost 700 people a year.

I am going to talk primarily about breast cancer testing, because 80 percent of the people who have come to see us for cancer have come because of concerns about breast cancer and breast and ovarian cancer. About 120 had BRCA gene sequencing in 2006, the $3,000 test. Then, we see a smaller number of people that take the single-site test, a number that is rising primarily because once you identify a specific mutation in one person, you start to see and check other family members for that genetic change. From one family that we identified 18 months ago, we have already seen 20 members for genetic counseling. We have identified somebody in that

family who carries two mutations and one from another side of the family. So even with a known mutation, it can be very complicated. Then we have a much smaller number that take the multisite test for the three mutations that affect the Ashkenazi population. In 2002, BRCA-1 rearrangement testing first became available, and as of August or September of 2006, the large DNA rearrangement test became available, so many of these people have had more than one test. As Dr. Ganz noted, there has not been the same demand for HNPCC testing, although that is increasing as well.

Although we see fairly high-risk families that have many members with breast cancer, only around 15–20 percent of our patients have deleterious mutations or a variant of uncertain significance. So, we are still dealing with whether we need to screen family members differently. We may tell them to come back and see us in 2 or 3 years because we think they are at high risk. We have a problem with variants of uncertain significance getting reclassified when we cannot communicate that we now know that the result does not mean anything to patients (or their families) because they are deceased or have moved.

We saw two sisters with premenopausal breast cancer at age 37 several years ago. One sister had ovarian cancer as well, but she was not tested initially. Her insurance wouldn't pay for it because she had terminal cancer. We tested the other sister with premenopausal breast cancer, and she had two variants of uncertain significance in BRCA-2. We tested her sister with ovarian cancer at that point, and she had a mutation and her sister didn't, even though she had premenopausal breast cancer. These two women died of their disease. Their brother came to us several years later. He told us that his sister had strongly encouraged him to have testing for the variant of uncertain significance. The variant had been reclassified, but up to that point we had not been able to find anyone to whom to report this. So, we are still reassessing whether we should be doing anything because of the other sister's mutation—just an example of the complexity of testing.

Most of the women who are having this kind of testing at our clinic are between the ages of 48 and 52. Those testing for a known mutation are a little bit younger, because they are likely to be daughters or sisters, as compared to an affected person who may be older. We have some men. We have a hard time getting insurance to pay for testing for men even when there is a known mutation, because the health benefits to men haven't been elucidated yet. So most of the men we are seeing are in families with known mutations or men with male breast cancer where we are doing gene sequencing. We have not found many of those with breast cancer with mutations.

Box 2-1 is a list of some of the other conditions we see in our clinic. If a woman has an early history of breast cancer and she tests negative for BRCA-1 or -2, we may think about Li-Fraumeni syndrome, Cowden syndrome, or Peutz-Jegher syndrome. So these patients may have many tests. This can be particularly true with the colon cancer syndromes. You may begin with FAP or attenuated polyposis associated with tumor suppressor genes APC or MYH respectively, and you may do tumor testing first. So there is great complexity in the kinds of tests we are offering. This results in the counseling being very time intensive and a great deal of time being spent with the family.

Myriad Genetics Laboratory is one of our biggest providers of oncology genetic testing. According to 2006 data, they are now doing a thousand tests a week, and they have done over 100,000 tests to date. About 12.5 percent of their tests are positive, and their variant of uncertain significance rate is about 10 percent, but it is much higher than that for underserved populations and minorities such as African Americans, American Indians, or the Asian population. About 50 percent of their tests are ordered by genetics providers or genetic counselors, 40 percent by oncologists, and 10 percent

BOX 2-1
Inherited Cancer Syndromes

- Birt-Hogg-Dube
- Carney complex
- Cowden syndrome
- FAP/APC
- FAMM
- Juvenile polyposis syndrome
- Familial prostate ca.
- Gastric polyposis
- Hereditary clear cell RCC
- Hereditary paraganglioma syndromes
- Von Hippel Lindau
- Peutz-Jeghers syndrome
- Retinoblastoma
- Tuberous sclerosis complex
- Hereditary diffuse gastric cancer
- Hereditary leioomyomatosis and RCC
- Hereditary melanoma
- Hereditary mixed polyposis syndrome
- Lynch/HNPCC
- Li-Fraumeni syndrome
- MEN1, MEN1A
- MEN2
- Nevoid basal cell carcinoma
- Wilm's tumor syndrome
- WAGR
- Xeroderma pigmentosa

by other health professionals. I certainly see more and more people now for whom I am providing the interpretation of test results that were ordered by another health provider. I see women who have variants of uncertain significance, who have been told they should have a mastectomy when they probably have a benign polymorphism, and I have seen women who have been told their variant probably doesn't mean anything when it probably does, and they are at high risk. Even looking at just the family history, that should have been clear.

Turning now to the training of genetic counselors: there are 27 programs that are accredited by the American Board of Genetic Counseling. There are three that have what we call provisional status; they are most likely going to be programs, but they are going through the application process. These programs are not evenly distributed; they are mostly in the eastern states and the Midwest. We would love to have a program in the Pacific Northwest, but for various reasons that has not happened. There is not easy access to genetics training around the country, so people have to travel, and that causes expenses and relocation of families and affects the demographics of the people who are likely to apply to these programs.

Accreditation involves 27 areas of competency within four critical domains. There is course work and over 800 hours of field work, so these are people that have had a lot of clinical experience. They all have to have teaching experience, and most of the programs require a thesis or at least some sort of research project, and they are mostly 18 to 24 months, although the Hopkins program is 3 years.

The genetic counseling workforce is primarily Caucasian and 95 percent women. We would like to change that. It is a very young workforce: 70 percent are under the age of 40. Sixty-seven percent have been in the field less than 10 years. There are good employment opportunities for genetic counselors; 75 percent are employed within one month from graduation. I should emphasize that all the genetic counseling training programs require training in cancer genetics and a placement in cancer genetics, so this young workforce is probably more able to deal with cancer genetics than some of the more experienced counselors if they haven't sought retraining. There have been some great opportunities. City of Hope offers an intensive cancer screening course. Memorial Sloan-Kettering Cancer Center has offered several programs. The National Society of Genetic Counselors has training every year, including cancer genetic training.

Genetic counselors practice in a variety of settings, just like other health professionals, but most genetic counseling is at academic health centers.

Few genetic counselors are in private practice, most are working with geneticists or oncologists in the cancer genetic setting. Forty-eight percent start at a university medical center, 28 percent in a private hospital, and 13 percent in public hospitals or medical facilities. I think it is very interesting that Myriad Genetics Laboratory has 36 genetic counselors working for them now; they started with one counselor in 1998. Private practices and HMOs each employ about 1 percent.

The genetic counseling profession has moved to meet the demands of health professionals and patients. Most genetic counselors are in prenatal counseling, but cancer genetic counselors are the next most numerous, and the distribution among the various fields of counseling has been stable. It does not appear to me that the workforce is moving from one field to another, raiding one genetic counseling specialty for other opportunities. I think genetic counselors are in the field of cancer genetics because that is what they are interested in. There are about 533 people in what we call our cancer special interest group. These are people that are actually paying extra dues to join that group, so there are probably additional genetic counselors that do some cancer genetic counseling but have not joined the interest group.

The number of patients a genetic counselor might see in a week is not as much as we would like it to be. That is due to the time-intensive nature of genetic counseling for cancer, not for lack of referrals. The general noncancer genetic counselor might see about 12 patients a week (9 new and 3 return), and in the cancer realm that might be 6 to 9 patients a week (5 to 6 new and 3 to 5 return). That is similar to other genetic counseling specialties that focus on one disorder, as compared to the more high-volume prenatal diagnoses.

Genetic counseling is complicated, because a complete family history is necessary. That is one of the reasons why the volume is not greater. I think it is irresponsible to order a genetic test and not have taken a family history. Unfortunately, I see that often from nongenetics providers whose testing is not necessarily done in the context of the family history. Certainly the interpretation is not done in that context. These are complicated patients. We take multigeneration pedigrees. For prenatal genetic counseling, it might be a three-generation pedigree, because you are just worrying about the parents and maybe the grandparents, but for cancer genetic counseling it might be four or five and six generations, if possible. We might also want to explore environmental exposures that could be contributing, such as tobacco use or even occupational exposures.

We do multiple tests with the breast cancer patients. We might start with sequencing and then do the rearrangement test or start with the Ashkenazi multisite screening panel, then gene sequencing, then the rearrangement test. In colon cancer testing, we might start with tumor tissue, then move to targeted testing, then a rearrangement test, and then we do MYH testing or something else. So, it is quite complicated. Also, we start with an affected family member first, if we can. For example, if a woman comes in and says, "I am worried because my father has had colon cancer," then we want to see the father if he is available and get the testing done on him, or the aunt or uncle. Those high rates of variants of uncertain significance I mentioned earlier are even higher in colon cancer testing currently, because fewer people have been tested. We often need to recontact families if we can when new genetic tests become available. And the tests are expensive, costing as much as $3,000, $4,000, or even $5,000 each. Patients may want to have insurance preauthorization done before they begin testing, and they may still be responsible for 20 percent of a $3,000 or $4,000 bill. This limits who can be tested.

Almost every person who comes in for genetic counseling for cancer is afraid of discrimination in insurance—health insurance or life insurance. I am hoping that the new genetic discrimination bill will provide some reassurance to people on that score. Another problem is that a negative genetic test may not reassure a person. Sometimes when patients from families with a known mutation are told there is good news, you do not have this mutation, they are disappointed because they wanted the reassurance of the breast MRI or the colonoscopy. In the face of a strong family history of cancer, a negative test may not be reassuring. So you have to counsel people as to what the results mean.

Genetic counselors are very busy, and not just doing cancer genetic counseling. About three-quarters work overtime, two-thirds without compensation. They are very active in the community, speaking to lay groups and serving on support groups or advisory committees. Genetic counselors are a part of the FORCE support group that Dr. Ganz mentioned. They are involved in writing genetics curricula, doing workshops for patients, and publishing, even though many of them do not have academic titles. A lot of them are teaching genetic counseling to students and to physicians, nurses, health professionals, undergraduate and graduate students, and social workers as well. So this is a workforce that is not only seeing patients, but helping to educate primary care and other providers about family his-

tory and genetic testing. It is important that this workforce be expanded for that purpose as well.

At one time, genetic counselors were certified by the American Board of Medical Genetics, as were geneticists. In 1993, the genetic counselors formed their own board, the American Board of Genetic Counseling. Since that time, the number of genetic counselors certified each year has almost doubled—to just under 400 in 2005. Unfortunately, we are not doing as good a job of getting new M.D. clinical geneticists or laboratory geneticists in the field. Those numbers are flat at around 100 per year. The board cycle is August, and 415 genetic counselors and 97 geneticists are signed up to take that board. There is also certification for advanced practice nurse genetics. I am not sure how many are certified, but I think there are fewer than 100, perhaps closer to 50.

Dr. Parkinson: What happened to the Ph.D. geneticists?

Dr. Weitzel: The American Board of Medical Genetics decided they were no longer able to maintain certification. There were only a couple of hundred at any given time for boards, maybe 30 or 40 Ph.D. geneticists are clinical counseling geneticists, and from the standpoint of cost, maintaining certification for such a small group was inefficient. So they stopped offering the board I think last year or the year before.

Ms. Debra Lochner Doyle, Manager, Genetic Services Section, Washington State Department of Health: They had to, because the American Board of Medical Specialties didn't recognize Ph.D.'s.

Ms. Bennett: The current genetic counseling programs are primarily in academic medical centers, and they are mostly in public schools. The number of students in a genetic counseling program ranges in each class from 6 to 8, although some classes in the larger programs have 20 to 22 students (average 16). There are about 515 applicants a year to genetic counseling programs; they are very qualified with high grades and good scores on their Graduate Record Examinations (GREs). They take the same board in the beginning as the physician geneticists, and then they take a genetic counseling exam. Programs are limited primarily by the slots in field placement because of that intensive requirement for training. This can affect enrollments; if a field site decided not to take a student that year, then enrollment in the program might have to be reduced.

The programs are not funded well enough to offer many scholarships, so that is part of the reason for low minority enrollments. There is an enormous volunteer effort supervising and teaching these students that is not compensated; most of the people doing the training are volunteers. The average cost to train a genetic counselor is about $35,000, more in a private school. That doesn't include any of the physical resources or some of the in-kind staff contributions from ancillary personnel that are involved. If we were going to increase the number of genetic counselors, there are several things we could do. All of the genetic counseling programs that exist today are willing to expand. They think they could double their volume if resources were available. There are at least five programs, including some in the Pacific Northwest, that could start operations, but there is no funding to apply for, so universities have to want to get into this field with their own resources. Increased funding for these programs would increase diversity of the workforce doing genetic counseling and increase clinical access, and also increase the number of people that are available to educate other health professionals.

The funding that is needed is not large; most programs thought that a startup fund of a few hundred thousand dollars would be enough. That would cover, as an example, a full-time equivalent (FTE) $100,000 genetic counselor faculty member and a FTE faculty medical geneticist with full benefits and joint appointments with other departments, added training sites at $3,300 travel stipends per student and supervisor stipends at $2,600 per student. Research funding initiatives would help to look at what matters in genetic counseling: are there different models of genetic counseling that could be used that are less time intensive, what is it that is most important about genetic counseling, are there any risk assessment tools that could be used that can identify these high-risk people in the first place, and what is the best age to test people? Is it really good use of your resources to test an 18-year-old or a 70-year-old? Is there a best age to offer testing and counseling that would give those with a particular disorder the most risk-reduction benefit?

In an ideal world, it would be great if all of our patients were well educated, knew their family history, acted on our advice, and shared this information with their families. But in the real world, it is very difficult to predict who will want our services, who will act on them, and who will share our views about the important issues that should concern them.

In summary, I think that cancer genetic services will continue to increase. It is difficult to predict the demand, but there is obviously a

demand for breast cancer services, and I think that demand will increase for colon cancer as well, as we learn more and can offer more. Genetic counselors are experts in this field. They should be among the people who are providing these services, although they are not the only people. It is essential that there be some national attention to supporting the training of genetic counselors, because there is definitely a way to increase the workforce that is not being addressed. We would like to increase the diversity of the genetic counselor workforce, and I think that would improve the diversity of our clients. If genetic testing became more easily available or readily accessible, it wouldn't mean that testing became any less complex. I do not know if we will ever be able to reduce the amount of time that is needed, because human communication does take time, and when you are considering having your breasts, ovaries, or part of your colon removed, that needs more than a 15-minute conversation.

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics, National Cancer Institute: What proportion of the demand for genetic counseling is cancer related and cancer relevant? Also, you mentioned the concerns about the age at which someone gets the genetic testing and counseling. What do you do about the syndromes that involve childhood cancers? Are there some special concerns or guidelines?

Ms. Bennett: In our center, we have a children's hospital that sees some of those families, but we do get requests for testing for BRCA in children. There are some standards about testing children if you are not going to do anything, if there is no health benefit for them at that point. So we do not offer it. The American College of Medical Genetics does have a general policy about testing children when there is no health benefit to them, but it is not specific for cancer. There are reasons to test children for FAP, Li-Fraumeni, or von Hippel-Lindau. However, I am aware of children that have been tested by a woman's obstetrician. The mother had a mutation, and her children got tested through a primary care clinic. I think those instances are unfortunate; it would be nice to manage this area better. In our clinic almost half of the patients are cancer related—second after prenatal. We are an adult clinic. I am aware that there are some demands for prenatal testing for BRCA-1 and -2. There have been requests for prenatal testing for Li-Fraumeni syndrome, and preimplantation genetic diagnosis is being requested, but there is not a huge demand for such services.

Dr. Mark Greene, Chief, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, NCI: In the current professional activities reports from the National Society of Genetic Counselors (NSGC), one survey focused on the people who do primarily *cancer* genetic counseling. Approximately 10 percent of respondents to that survey indicated that they were thinking of leaving the field, and another 20 percent were apparently undecided, but it was an option under consideration. It suggested that not only is there a problem recruiting people to become genetic counselors, but there are real issues related to retention. Would you comment on that, please?

Ms. Bennett: Part of the issue is the demographics of genetic counselors. They are primarily young women, and they are leaving the field to have their families and may not return to the field, or may not even return to the workforce, at least not in the times that we have surveyed them. In general, there is surprisingly high satisfaction with genetic counseling. The main things that genetic counselors aren't satisfied with are salary and opportunities to advance. I think those are the main reasons why people leave.

Dr. Samir Khleif, Food and Drug Administration: I am going to ask about a different level of complexity that we might not have an answer to, but I would really like to discuss. You mentioned that this is a family issue and not an individual issue. Some of us have to deal with this in different countries. Families in some countries include 5,000 or 10,000 people. In a country like Jordan, where we helped to build the cancer center, first cousin consanguineous marriage is 25 percent, and in some instances 50 percent. How would that affect your management?

Ms. Bennett: We are having a meeting May 2 in Seattle to talk about consanguinity, and one of the things we are looking at is cancer policies and cancer risks related to that. I think the key is how you define a family—there are some families where there may be multiple fathers, five or six partners, and all the children are half siblings. Some family history questionnaires ask if your aunt or cousin had cancer, but how people define aunt or cousin is different in different countries. I don't know if that answers your question.

Dr. Khleif: The definition is sometimes unclear when you have a family that has had first cousin marriages for the past 10 generations.

Ms. Bennett: Right, so I don't think the whole issue of consanguinity in cancer has been completely explored, but we are trying to address it.

Dr. Roy Herbst, Chief, Section of Thoracic Medical Oncology, M.D. Anderson Cancer Center: I was impressed that the sequencing is so expensive, especially with that test becoming so much more routine. I would like to know why that might be, and also, what part of that fee comes back to support the genetic counseling program, which is so vital for cancer care?

Ms. Bennett: It is because of the patent on the gene. Most sequence tests for other genes are anywhere between $600 and $1,200.

Dr. Herbst: Is the company under any pressure to feed back some of that money to support your program? You would think with more and more testing being done, it is vital.

Ms. Bennett: One of the big issues is that people want these expensive tests. It is time intensive for us to take the extensive family history to ensure that the proper member of the family gets sequencing. As I mentioned earlier, we often tell the family member making the appointment that we would like to see some other family member first, since it appears that that person should be the one to be sequenced. Our total patient volume has been stagnant for 2 years at about 1,400, and cancer volume has also been stagnant. That is because we are not getting more resources, it is not because the demand isn't there. Rather than feeding back to support our programs, there is a pretty aggressive push by one of the commercial companies to persuade clients that they don't need genetic counseling; anyone can order this test.

Dr. Weitzel: It is worse than that because the counselors who need to be doing the counseling are doing business. My counselors are spending an inordinate amount of time figuring out how to get the expensive test covered by insurance. What happens is, because the companies don't discount the test either, we have to do it as a third-party transaction. We draw the blood, send it out, but we don't bill for it. The company bills directly to the patient. If we billed for it, we would be subject to our managed care contracts, 30 cents on the dollar. The company is not going to discount it, so I could lose $2,000 on every patient. As I said, the result is that my counselors are spending time trying to get the insurance and billing taken

care of when they should be spending more time on care of the family and counseling, and that is an inefficient use of our expert workforce.

Dr. Thomas Burish, Provost, Notre Dame University: Experience has shown that whenever someone has the appellation *counselor*—sex counselor, marriage counselor, psychology counselor, genetic counselor—lots of unqualified people call themselves counselors, which makes some kind of certification essential so the public can distinguish people who are trained as counselors and those who are not. How big a problem is this in genetic counseling, and what is the solution to it?

Ms. Bennett: I think it is a big problem because of the commercial push for testing. People have said you can be a genetic counselor if you complete a short course, a one-day work session kind of thing, which is very different from some of the more intensive courses that are available. There is a big push for licensure of genetic counselors. Any statements against it have been from people who aren't trained but want to call themselves genetic counselors. But licensure has been hindered because to institute that there has to be evidence of harm from improperly trained people who are allowed to practice in the field and order genetic tests, and that evidence is not so easy to obtain.

Ms. Lochner Doyle: The number one complaint that I get is not about these other "counselors" calling themselves such, it is about primary care providers offering a service that they are not really competent to provide. And of course, you cannot reduce the scope of practice of an M.D.

Dr. Burish: What is the solution, and who should take responsibility for implementing it?

Ms. Bennett: I think licensure would help a lot, and that would be at the state level. We already have a national board test by the American Board of Genetic Counseling, but that is a test of competence and training, not a license to practice. On the federal level, however, there is a move to have CMS recognize genetic counselors the same way they recognize physicians' assistants.

Dr. Ganz: Physicians are the problem, because any oncologist, primary care physician, or obstetrician/gynecologist can order a blood test. But if

you have not done the pretest counseling, which includes both the medical and the psychosocial implications, and you are not prepared to do the posttest counseling to inform people about the results, then they wind up with a certified genetic counselor who has to clean up and do what did not get done. A very simple example would be to draw a blood test for prostate specific antigen (PSA) without informing the man that you were doing a screening test for prostate cancer and then have the test come back positive. That happens all the time. It would be good if the man was informed that among the other things that I am testing for today, your cholesterol, your blood sugar, I am also doing a screening test for prostate cancer, which could have the following implications. It doesn't happen.

Ms. Lochner Doyle: To get back to the demand questions, I am wondering what is the average wait time before those who call can actually get an appointment?

Ms. Bennett: Our problem has been even getting the referral calls returned because we don't have the secretarial help. The whole structure needs to be supported, the billing and the other support needs. Nevertheless, the wait time in our clinic to see a genetic counselor is maybe 2 weeks—to see a geneticist it could be 2 to 3 months.

Dr. Ganz: We are moving to a different business model exemplified by breast cancer patients who are now making decisions about treatment and what they are going to have done. You have to look at the whole package or system of care that is being delivered to the patient. If a woman is going to have a genetic test done and, as a result, is going to opt for preventive mastectomy and immediate reconstruction, the plastic surgeons are going to benefit from the appropriate and timely diagnosis of the patient, and the whole system would have the resources then to pay for this appropriate care. I think if we are going to afford this, this is the way we do it, but it is not in our system now.

Gail Javitt, Esq., Law and Policy Director, Genetics and Public Policy Center, Johns Hopkins University: Implications of Home Tests and Direct-to-Consumer Advertising: I am going to talk about the policy implications of direct-to-consumer (DTC) genetic testing, particularly focusing on tests for cancer. DTC genetic testing actually means different things to different people. There is DTC that is advertising only—to

promote awareness and demand—and the test must be ordered by, and delivered to, a health-care provider. Then there is DTC in which everything is DTC. Consumers can order the test without a doctor and get the results without a doctor. And finally, there is a hybrid, where consumers order, generally through a website, without the involvement of their own health-care provider, but there is a counselor and/or provider on the staff of the company that is providing the service who authorizes the transaction. The results go straight back to the consumers without going to their personal physicians.

The only example of advertising-only DTC I am aware of is that of Myriad Genetic Laboratory, which ran an ad campaign in Atlanta, Denver, Raleigh-Durham, and Seattle for BRCA tests in 2002 in order to raise awareness about the importance of early disease detection. There have been some studies about what impact that had. The CDC did a phone survey that showed increased awareness in the cities where the advertising campaign was piloted but not necessarily more interest in getting tested (Genetic testing, 2004). There was also a Kaiser mail survey showing a small negative impact in terms of anxiety and an increase in inappropriate testing (Mouchawar et al., 2005).

But other than that example, the trend in DTC has been both advertising and sale of tests. There are many examples not related to health care that I am not going to focus on: ancestry and paternity testing, for example. There are also tests that are health related and health profiling—for disease-related genes, predictive genes, profiling, pharmacogenetic tests, tests for your heart health, your bone health, and even tests for athletic performance that help determine which sport is right for you.

Reporters frequently ask me whether DTC advertising is growing. Certainly in terms of the different types of tests that are being offered, it has grown since we started looking at it. Whether more people are getting tests is more difficult to know. Tests range from the typical genes that are well accepted by health-care providers—cystic fibrosis, factor V Leiden (a blood coagulation abnormality), and athletic performance as I just mentioned; so these tests cover a wide range of purposes. My favorite poster child for DTC is the baby gender test, to give you the extreme end of the spectrum, which purports to detect fetal gender as early as 5 weeks of pregnancy by detecting free fetal DNA in the mother's blood, which apparently works less well than when my grandmother used to look at our bellies and say boy or girl.

I went back and looked through the tests that are available and advertised in order to identify which ones are being offered specifically for cancer,

and found four examples: BRCA testing, CyP2D6 testing for tamoxifen dosing, colon cancer screening, although not HNPCC, and nutrigenetic tests that make some cancer prevention and cancer risk claims. DNA Direct happens to be offering three out of these four examples (although the tests themselves are performed for DNA Direct by Laboratory Corporation of America), so I will be spending a little time discussing their website so you can get a sense of what claims are being made.

This company offers testing for the BRCA mutations. The site offers a choice of full sequencing, multisite testing, and single-site testing. It says that full sequencing is appropriate when you are the first person in your family to test and you are not Ashkenazi Jewish. It says that multisite testing looks at the three specific gene changes in the BRCA-1 and -2 genes that are associated with most cases of hereditary breast cancer in people of Ashkenazi Jewish ancestry, and that single-site testing is done when a specific BRCA gene change has been identified in your family. I'm not drawing conclusions on the merit of these claims. You are the doctors and experts, and you can draw your own conclusions.

The website provides an online questionnaire that the consumer takes in order to determine whether to test and what test is appropriate. I didn't try every single permutation, but I tried two. If you fill out the risk factor questionnaire saying no to every risk factor except that you are Ashkenazi Jewish, it recommends multisite testing. That costs $695.

Dr. Greene: And that recommendation is made even in the absence of any history of cancer either in yourself or your family?

Ms. Javitt: That's right. If you say no to everything except Ashkenazi Jewish ancestry they still recommend testing. You receive a personalized report. The company states that it has board-certified genetic counselors on staff and provides posttest consultation as part of the service. If you fill out the online questionnaire answering no to every question except that you were diagnosed with breast cancer after age 50—for example, no to any family history and things like that—the site recommends full gene sequencing because you are the first person in the family to be tested, and you don't have Ashkenazi Jewish ancestry. The cost for that testing is $3,456, including a personalized report and phone consult.

There has been recent evidence that women with certain variants in their cytochrome P450 2D6 genes had a shorter time to recurrence of breast cancer after treatment with tamoxifen, a hormonal therapy to

reduce recurrence of some breast cancers. Recently an FDA advisory panel recommended a change in the label, saying that some women with certain variants of 2D6 may be poor metabolizers of tamoxifen (to its active form, endoxifem) and thus at higher risk of breast cancer recurrence, and that genetic testing is available to help determine this. Studies have not shown that prospective genotyping for 2D6 prior to selection of therapy improves outcomes, and the FDA has not yet made any label change. Nevertheless, DNA Direct is offering 2D6 testing for women taking or considering taking tamoxifen, claiming that genetic testing can predict whether tamoxifen is likely to be an effective treatment. That is $300. My very cursory understanding is that there is a lot of controversy about these findings. They are from small studies, and clinicians are not yet routinely testing for this purpose, but yet a woman can be tested through a DTC route.

There is another site, Genelex Corporation, that offers an extended CyP panel for $1,000. The company is not making specific tamoxifen claims. Its claims are limited to antidepressant efficacy; that is, that testing for CyP variants can aid in drug selection and dosing. The AHRQ just issued a report concluding that there is a lack of data supporting a benefit for CyP testing for antidepressants. So you could, if you were a woman who knew about it, also get CyP2D6 testing from this site as well.

My third example is for colon cancer screening, also offered by DNA Direct. This is a screen for 23 DNA markers that the company states are associated with colon cancer and precancerous polyps. These are mutations in the APC, K-ras, and P53 genes, one microsatellite instability marker in BAT-26 for HNPCC like colorectal cancer, and one long DNA marker. I filled out the online questionnaire as if I were an applicant who was under age 50 without risk factors; the response said I was at general population risk and recommended the PreGen-Plus as a noninvasive option for interim screening, either between colonoscopies or if colonoscopy is declined. That is $575. From facial expressions here, I gather that is not a persuasive case.

Dr. Greene: Is PreGen-Plus a blood test?

Ms. Javitt: No, it is a stool test. They don't get too explicit about how you collect your sample at home.

Ms. Bennett: I ordered a kit once. It is a large box.

Ms. Javitt: The final example is the nutrigenetic test that makes diet and lifestyle recommendations based on testing a 19-gene panel. One of the groups is for antioxidant detoxification, looking at variants in six different genes. The claim is that these variants may reduce removal of toxins from the body that can be associated with cancer. Based on your profile, they recommend that you eat certain vegetables and fruits and avoid tobacco smoke or stop smoking. Some companies recommend certain supplements. Based on my looking at two examples, prices appear to vary between $300 and $400.

Nutrigenetic tests have been covered in the press recently because of a report that the Government Accountability Office (GAO) issued last summer, and the hearing that was then held by the Senate Special Committee on Aging, looking at the nutrigenetic tests from four companies, although one lab was doing the tests for three of the four. The GAO report concluded that the tests they purchased made misleading predictions that were medically unproven and so ambiguous that they were not providing meaningful information to consumers. On the same day, the Federal Trade Commission (FTC) issued an alert that said essentially, "Buyer beware," and explaining that some of the tests lack scientific validity and others provide results that are meaningful only in the context of a full medical evaluation.

Who is using these tests? This is a question we would really like to answer, but there are very few data. At the most recent American College of Medical Genetics meeting last week, a group from CDC reported on a survey of 5,000 consumers and a separate survey of health-care providers (both on nutrigenetic testing). Among consumers, they found 14 percent were aware of nutrigenetic tests, and 0.6 percent had used them. Among providers, 44 percent were aware, 41 percent had never had a patient come to them asking about these tests, and 74 percent had not discussed results with patients. Nevertheless, the population estimate based on 0.6 percent is about 2 million. So even though it is a small percentage, a lot of people are apparently using these tests. The CDC will go on and do a broader survey and refine their instrument to try to get a better idea of who is using these tests. As far as the other DTC tests, we do not have much data about who is using them; the companies have those data, but they are not necessarily sharing them.

To put this in context, the number of conditions for which there are genetic tests now exceeds 1,300, not just for cancer but overall, and continues to grow. DTC testing is just a method of marketing the tests. As the number of tests grows, the potential number of genetic testing services

offered directly to the consumer grows as well. The gene test laboratory directory now comprises slightly over 600 labs.

Let us discuss regulation. Is there government oversight of genetic testing? Not just DTC testing, but genetic testing more broadly? There is some, but there are lots of gaps. Who are the players who could, are, or should be involved in overseeing genetic testing? At the federal level they include the FDA, CDC, and CMS. They each have a piece of the puzzle, but there are lots of pieces that are not under any of their jurisdictions. The FDA, as you all know, regulates drugs, devices, and biological products as well as human tissue, and they are the device authority that is potentially in play when it comes to genetic testing. The CDC serves in an advisory capacity to CMS over the implementation of something called the Clinical Laboratory Improvement Amendments of 1988, or CLIA, which give CMS authority to certify all clinical laboratories and set standards for them, including quality control and quality assurance standards, as well as personnel requirements.

A clinical laboratory under CLIA's jurisdiction is any lab that examines materials derived from the human body in order to provide information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. Genetic testing labs are clinical laboratories if the result is being returned to a patient, clearly. There is a basic group of requirements that all genetic testing laboratories must meet, including validation and documentation of procedures, personnel, and the like. Furthermore, because genetic tests are complex, the labs are considered high-complexity laboratories by CMS. Most high-complexity laboratories under CLIA are subject to something called a specialty area, which means there is a specification of quality control and personnel requirements, and, perhaps most importantly, proficiency testing requirements. That involves the laboratory analyzing test specimens that are sent to it to assess the accuracy of its determinations. However, there is not a specialty area for molecular and biochemical genetic tests, and there is no clear mandate under CLIA that genetic testing laboratories perform proficiency testing. The CLIA regulations also do not cover clinical validity. The regulations have been implemented to focus on laboratory performance, not tests for clinical validity.

The issue of CMS oversight for genetic testing has been examined for about 10 years. The Genetics and Public Policy Center is not the first one to examine this. There have been recommendations from a combined National Institutes of Health (NIH) and Department of Energy (DOE)

task force (1997) and from the DHHS Secretary's Advisory Committee on Genetic Testing (2000) for strengthening oversight at both the FDA and CMS. The CMS issued a notice of intent to develop a specialty area for molecular and biochemical genetic tests in 2000, and in April 2006 it got as far as putting it formally on their regulatory agenda with a release date of November 2006. However, in September 2006, CMS announced that it would not be issuing a specialty area. At that point, we, along with two other organizations, filed what is called a petition for rulemaking, formally asking the agency to issue a rule for a genetic testing specialty.

We wanted to know how the genetic testing labs were performing; maybe a specialty area really does not matter. We fielded a survey of clinical genetic testing laboratories (Hudson et al., 2006) and received responses from 190 laboratories. Only two-thirds of those surveyed reported participating in all available proficiency-testing programs, such as, for example, the formal program from the College of American Pathologists that sends out test specimens and grades performance. In the absence of a formal program, there are informal ways such as sharing with another laboratory or splitting samples. We asked, if a formal program was not available, does the lab use some other method, and almost a quarter said they did not always perform proficiency testing using some other method. We also asked the labs what has been their most frequent type of error in the last 2 years, dividing the responses into errors that could be considered preanalytic, analytic, or post-analytic errors. A strong predictor of whether analytic errors were the most common was how much proficiency testing laboratories did.

Dr. Greene: How did the labs determine they had made an analytic error?

Ms. Javitt: It is self-reported error. Under CLIA you are supposed to keep records of errors you are aware of. Sometimes it is hard to know. The laboratory does not always find out.

I mentioned that the FDA also has a piece of the puzzle. The FDA regulates the components that laboratories use to make tests, general-purpose reagents, and also a class of reagents that the agency has categorized as analyte-specific reagents (ASRs), which they consider to be the key ingredient of an assay. Regulation does not mean clinical validity of that component is monitored in this case; rather, it is what is claimed for the component, whether it is made under good manufacturing practices and is sold only to appropriate laboratories. In a draft guidance document, the FDA recently cracked down on the way the ASR provision has been used;

the agency means it to apply only for single analytes. Some vendors have been combining their ASRs in labeling, instructing use of one ASR with another—that is, selling a test kit. A test kit is a package of reagents with labeling and directions for use that a laboratory can use to perform a test, in our case a genetic test. Test kits are also subject to FDA regulations. Those regulations involve more than just looking at labeling and good manufacturing practices. The FDA reviews the analytic and clinical validity of the test kit. Either premarket notification, which is like premarket review, or something more formal called the premarket approval application is required.

Only a few genetic tests, about five or six, have gone the test kit route and been approved by the FDA. Otherwise, of the more than 1,000 genetic tests, the vast majority are what are termed *laboratory-developed assays* or home brew assays. The FDA has gone back and forth regarding jurisdiction over laboratory-developed tests. Currently they are exercising what they call enforcement discretion and not looking at them, although they have recently issued a fairly controversial draft guidance document on a class that they have called *in vitro diagnostic multivariate index assays* (IVDMIAs). These have particular relevance for this discussion, because the first example of an IVDMIA was a test that claimed to determine whether a woman is likely to have a recurrence of breast cancer. The Oncotype DX assay is claimed to analyze the expression of a panel of 21 genes and predict the likelihood of recurrence of stage I or II estrogen receptor positive breast cancer. The FDA is concerned about this type of test, because it examines multiple signals and then uses an algorithm (which is not transparent to the clinician) to make a treatment decision. In view of this, the FDA is considering the assay a test kit, even though it is developed by a laboratory and would traditionally have been lightly regulated.

Dr. Greene: Is this similar to the FDA action taken against the OvaCheck proteomics assay?

Ms. Javitt: An IVDMIA does not have to be a genetic marker. It could be any type of marker where you take multiple signals and analyze them. One can conceptualize these regulatory approaches toward home brew tests, home brew tests with ASRs, and test kits by using baking a cake as an example. If you buy the box of Betty Crocker cake mix off the shelf, and you make a cake, that is a test kit. The mix goes to the FDA. If you are pooling the eggs, flour, and other ingredients together on your own, it is a

home brew, and the FDA has no involvement. If you are using Hershey's chocolate (an ASR) with the generic ingredients (a home brew), the FDA looks at the ASR. So, you can use the same test but use a different way of getting the test, and have vastly different regulatory structure.

Dr. Parkinson: And business model, I might add.

Ms. Javitt: Right, that is a good point. The home brew test is under CLIA, but CLIA is looking at the kitchen, not at the cake. In the absence of a genetic testing specialty area, CLIA regulators are restricted in how they look at the kitchen. If it is an ASR you get kitchen inspection plus ASR oversight, and then finally if you are a test kit maker you get CLIA and the FDA oversight. These different degrees of regulation have implications for the cost of test development and pricing.

The FDA, despite having a relatively low level of oversight for genetic testing, has started thinking about how genetic information can improve drug development and therapy and improve safety and effectiveness of drugs. The agency has issued several guidance documents, including a final guidance on pharmacogenomics data submissions in 2005 and a draft guidance for pharmacogenetics tests and genetic tests for heritable markers in 2006. These have been primarily aimed at the drug side, requesting data about genetic markers that affect drug efficacy and safety. An IVDMIA draft guidance in 2006 looked at the device side of things, in an attempt to strengthen oversight.

How does the FTC fit in here? They are not a DTC test regulatory agency, but they have generalized authority to prohibit false and misleading claims or anything that creates an unfair or deceptive trade practice. They have not taken any enforcement actions against DTC companies. In one instance, we know that complaints were filed about the Baby Gender Mentor case, but other than the consumer beware document that I mentioned earlier, FTC has not intervened in nutrigenetics testing. A class action is underway against Baby Gender Mentor, so maybe the tort system will help us here.

We mustn't forget about regulation at the state level. State governments oversee the practice of medicine generally. Different states through their laboratory practice laws also regulate who can order a test and who can receive the test results. So that affects whether you can do DTC testing in various states. About half the states allow a laboratory to receive a sample directly from a patient and return the result. Further, on Baby Gender Men-

tor, New York prohibits DTC testing and has sent letters to Baby Gender Mentor (located in Massachusetts) warning against selling in New York. The company would be liable for fines every day. In practice, that is a very hard thing to enforce, especially when dealing with Internet commerce.

Two professional societies, the American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) both have considered draft statements of policy on DTC genetic testing suggesting transparency or, in the case of ACMG, announcing that testing should be ordered, received, and interpreted by qualified health professionals. In theory, these societies could influence DTC practices.

When asked whether direct-to-consumer genetic testing is regulated, one needs to clarify, regulation of what? Regarding advertising product claims, that is the Federal Trade Commission's bailiwick. If it is a test kit, the FDA would have some involvement. If it is about clinical validity, the FDA evaluates it only if it is a test kit; CLIA does not. If it is about the laboratory, CLIA could establish a genetic testing specialty but has not. As the GAO report and the Senate hearing pointed out, some of the laboratories that were offering the DTC tests that came under scrutiny were not even CLIA certified, and there is not a transparent process for either doctors or patients to determine whether a laboratory they are using is CLIA certified. Whether labs can do DTC business, give a patient the results, get a sample from a patient without a provider intermediary—those are questions of state law.

Is DTC testing good or bad? There are arguments in favor of it and arguments against it, and I have tried to identify the issues. There is certainly a concern about false and misleading claims, and I have presented some examples. There may be a lack of counseling and context because there is no requirement that a company offering DTC tests provide counseling, although some do. There is the risk of inappropriate test selection, if the consumer does not have a provider or a counselor helping with that. An opportunity to get treated, for example, might be missed if the PreGen-Plus test provided an assurance that there was no risk of colon cancer, and the patient skipped a recommended colonoscopy. There is concern about laboratory certification and test validity. There is also a concern about the potential to undermine the relationship between the provider and the patient. For example, this could happen, if it hasn't happened already: a patient who gets the 2D6 assay might tell her oncologist that she feels she shouldn't be on tamoxifen. It is the wrong drug for her, and she wants a different drug because she is a poor metabolizer of CyP2D6. The provider may disagree. I think there is not consensus among physicians about whether this testing

is clinically useful. Certainly, there is an opportunity for tension between patient and physician. Finally, we should not forget about wasted money. Is it really necessary to spend $3,400 on whole-genome sequencing?

On the other hand, there are those that argue that DTC can increase consumer access to testing and give consumers more choice about what tests they get. It can also give them more information than they might otherwise have, and armed with that information they may seek treatment earlier. Perhaps an informed patient is a provider's best customer. Certainly an informed patient can improve the provider-patient relationship, and potentially, although it doesn't sound like it in some of the examples, testing costs might decrease if the clinician intermediary was eliminated. Privacy and confidentiality I put on the borderline between the pros and cons. This is because some of these DTC sites make claims that privacy is more protected through the Internet because results do not get in the medical record. As we heard earlier, there is a lot of fear about genetic discrimination. However, I question the premise that DTC testing necessarily is more protective of privacy. The HIPAA Privacy Rule specifically protects health information in medical records and includes significant penalties for misuse. Consumers may not know very much about the company they are sending samples to over the Internet, nor what legal protections for confidentiality and privacy they have. In addition, if patients receive a worrisome result they are likely to take that to their clinician and so it gets into the medical record anyway.

So why doesn't somebody just pass a law? There are two bills being considered in Congress at the moment. One, introduced this past month by Senators Kennedy and Smith, would give the FDA jurisdiction over laboratory-developed tests and would require CMS to issue a genetic testing specialty. It also would require the FDA to provide premarket review of tests sold directly to the consumer. Second, legislation that was just introduced by Senators Obama and Burr gives the secretary of DHHS a mandate to improve oversight and would direct CDC to study the impact of DTC genetic testing on consumers, among other things.

In summary, DTC is basically just a method of marketing a genetic test. A variety of concerns have been raised about it, but there are very few limits on its practice. It is also a good lens for looking at the state of oversight of genetic testing more generally and the gaps that exist. I think we can all agree that we would like accurate information to diagnose, treat, and prevent disease; that laboratories should be qualified; that providers

and patients ought to have adequate information about genetic tests; and that we need a regulatory system that encourages doing a good job, rather than the current one, where the incentive is to do less and not to go through the FDA. Overall, there is a need for risk-based regulation, because not every test is going to merit the same level of scrutiny. And there needs to be a mechanism for postmarket reporting so that we know when errors are occurring.

Dr. Scott Ramsey, Member, Fred Hutchinson Cancer Research Center: This is just to be a little controversial, but I will give you my economist's perspective on this. I think DTC and genetic testing are a little bit of a tempest in a teapot. Although we all can find anecdotes with people doing dumb things with tests, in terms of a major societal impact I'm not sure that DTC is ever going to be a big problem. The reasons are two, and they have to do with barriers to this market. The one barrier on the supplier side is the cost of advertising. Anybody can get on the Web and it is very inexpensive to advertise, but we know that the uptake of that in our society as an advertising medium is pretty modest. The other approach is through mass marketing, like Viagra at the Super Bowl, which is where you reach a lot of people, but the barriers to that are huge because the costs are huge. The biggest company in this whole field, Myriad, had a marketing campaign and spent millions of dollars. We haven't seen them do that again, and there must be a reason. They actually presented the data on their advertising at a genome conference that I attended a couple of years ago, and I asked the presenters how many more people did they get from this for these tests, and they wouldn't tell me.

Ms. Bennett: They are planning another one.

Dr. Ramsey: But these are going to be one-time shots. I think they are expensive, even for a company that size to undertake. The other barrier, which is not insignificant, is the cost to the individual. These aren't reimbursed by insurance in general, certainly not buying directly, where you bypass everything. This is not like buying clothes at Land's End. This is a very different product, and I think people pause before going to a website and ordering genetic tests. So there will always be people who will buy this stuff, but whether it rises to the level of something that we should spend an extraordinary amount of effort to control, I'm just not sure right now.

Ms. Lochner Doyle: I was intrigued with your pros and cons. Regarding the cons, I thought to myself, those are all true for regular genetic testing, not limited to direct-to-consumer testing. Just a comment.

Ms. Javitt: I think there is a commonality in these two points. I think we don't know what impact DTC is going to have; that is absolutely right. The CDC is trying to get some data on who is using it and what kind of effect it has. It may wind up being small. But we have looked at it as a real tool for looking nationally at the flaws in genetic testing oversight more broadly, flaws which I think are affecting the public health and need to be fixed. So it is serving that role, in addition to just being an interesting phenomenon.

Dr. Ferrell, Research Scientist, City of Hope National Medical Center: Just like Dr. Ramsey, to be the devil's advocate in this conversation and probably out of my ignorance, I have two comments. The primary reason that this didn't seem to be a public health concern is the market issue. It is so expensive that there is not a huge consumer demand. What if next year, there was a new business plan that delivered a very inexpensive technology? Then suddenly this would be a whole different picture that might have real implications.

Second, in this country we still have significant problems of people getting cancer information and diagnoses early in the course of their disease. As this field is explored, is there a potential or an opportunity, if these companies are going to mount their million-dollar campaigns to get their messages to the public about cancer, to send correct messages to the consumer about cancer? If DTC is part of our future, is there a proactive way to harness it that might help the things that we really care about in this field?

Ms. Javitt: I think the ASHG statement that is being worked on gets at that point: "Don't stop it entirely, but if we are going to do it, here are some guidelines for how to do it responsibly."

Dr. Greene: Delivery and Research Issues: Health-Care Provider Supply and Preparedness: I want to begin with a summary of the various levels at which health-care providers may interact with the genetic testing and counseling process to frame the discussion of the workforce issues that I have been asked to address. You have heard the sequence, beginning with a positive family history, followed by an effort to evaluate the significance of the family history with a subset of individuals being further selected for formal genetic risk assessment. Eventually some of the latter undergo muta-

tion testing and are found to be either negative or positive. Both groups require clinical follow-up and management. Both groups are potentially eligible to participate in clinical research studies, which is where my interest has been focused.

To get through this whole process involves a large cast of characters acting sometimes in concert and sometimes not. In contemplating the workforce that is available to participate in genetic risk assessment as a whole, we have a fairly diverse menu (primary care physicians, specialty physicians—oncologists, gynecologists, gastroenterologists, and so on—genetic counselors, advanced practice nurses, social workers, specialty surgeons, and clinical investigators). I suggest that, to the extent that this issue becomes something that the IOM continues to pursue, individual experts in each of the disciplines be asked to make a presentation like the one that I have been asked to make, so that you can get the level of detail that Ms. Bennett provided for genetic counselors.

For all its complexity and cumbersomeness, the system can work. I know this from my participation in a complicated study of women at increased risk of ovarian cancer who underwent either risk-reducing surgery (removal of the ovaries and fallopian tubes) or ovarian cancer screening. This study—GOG-199, the National Ovarian Cancer Prevention and Early Detection Study—has accrued 2,605 study participants nationwide during the past 3 years, an effort that has required participants from all classes of providers that I just mentioned.

We have already heard that physicians do not do a high-quality job collecting family history from their patients, and that they do perhaps even less well interpreting what those family histories might mean for clinical decision making regarding risk stratification and risk-specific interventions. There is literature that provides some information as to why providers neglect family history. Important factors cited include the excessive amount of time required to take an informative family history (in the context of busy clinical practice) and the fact that providers are not being compensated for that effort. Interestingly, physicians report having concerns about their genetic knowledge and skills, as well as their ability to interpret this information and accurately counsel patients. The lack of provider self-confidence is an issue that has not received much attention and, in my opinion, it is a powerful deterrent to engaging in genetic risk assessment. Most physicians are not comfortable doing something that they do not understand, have not mastered, and cannot address authoritatively. There is an even longer list of potential barriers to collecting family history data (see Box 2-2). The family

BOX 2-2
Barriers to the Collection of Family History Data

- Lack of time
- Lack of reimbursement
- Lack of genetic skills
- Lack of genetic knowledge
- Lack of self-confidence
- Lack of family history tools
- Lack of referral/management guidelines
- Uncertainties over insurance coverage
- Complexity of modern genetic testing
- Genetics prognosis and management issues
- Concerns over potential genetic discrimination

history is the cornerstone to the genetic risk assessment enterprise; without an adequate family history, effective risk assessment is impossible.

How big is the task that the genetics workforce must address? First, let me remind you that there is now a very large set of hereditary syndromes, more than 40, with known genes for which clinical testing is available in the routine health-care setting. The list is even longer if genetic tests currently available for research purposes are included. In addition, there are several hundred familial syndromes for which the susceptibility genes have not been identified, but individuals from those families still require risk assessment, counseling, and management. There is a huge group of families (precise size is unknown) with undifferentiated histories of uncertain significance that need to be addressed at some level. And finally, for the cancer patients and gene carriers, their family members require attention as well. There is no question that the demand side of this health-care problem is quite large.

The remainder of my presentation will describe the involvement of each of the major disciplines involved in providing cancer genetics services. One important current initiative is based on encouraging primary care practitioners to take an active part in clinical genetics and particularly to become involved in the earliest stages of filtering out those who have a family history that requires further evaluation from those that can be reassured and sent on their way. The American Academy of Family Practitioners (AAFP) has

invested considerable energy and resources in this regard during the past several years. It declared 2005 the Year of the Genome, and initiated a series of educational activities for its membership intended to remedy recognized knowledge deficits. A continuing medical education (CME) video series was made available to its membership that highlighted an approach to taking a good family history as well as modules on hereditary breast and colon cancer. A clinical genetics monograph was developed as part of its home education series that was mailed to all AAFP members. I am pleased to say that one of my staff members was the lead author on that piece, which was a general primer and introduction to clinical genetics. These are noteworthy accomplishments, but curriculum material related to genetics has yet to be fully integrated into family practice training programs.

In internal medicine, a bit more progress has been made. Considerable energy has been invested by a knowledgeable group of experts aimed at developing a curriculum outline to introduce medical genetics material into internal medicine training programs. That proposal has been published (Riegert-Johnson et al., 2004), but my impression is that it is making slow headway. In part, this is a consequence of modern clinical genetics being so complex and moving so quickly that it is difficult to formulate a curriculum that is not out of date by the time it is designed. Furthermore, the curricula into which this new material would be introduced are already jammed to overflowing; incorporating new material into established programs is not easy. The strategy that has been proposed (a good one given the complexity and pace of change) is to focus on vocabulary, concepts, and skills for lifelong learning rather than memorization of specific sets of facts so as to lay the foundation for self-directed future education.

Historically, genetics was rooted in the disciplines of obstetrics and pediatrics, and it evolved from the prenatal and developmental anomaly world. Most genetics training programs in the United States are pediatric or obstetric in their focus. Yet, the demand for the kind of services that we are considering today resides in illnesses that affect adult populations. In fact, adult-onset genetic cancer susceptibility disorders are being more and more widely recognized, and testing for these conditions is now becoming more widely available. Also, children who have pediatric genetic disorders are surviving into adult life and bringing their pediatric syndromes into an adult care setting in which the clinicians are completely unfamiliar with their disorders. Adult care providers are simply less educated and less prepared for this responsibility. In addition, there is an absence of concise diagnostic and management guidelines and atlases related to these syndromes that are

targeted at providers of care for adults. These tools have been invaluable in the pediatric setting in which, for example, illustrated textbooks of dysmorphology are available to provide a handy reference for disorders that are not routinely encountered. Most adult practitioners have not been exposed to these materials, communication with geneticists may not be optimal, and published guidelines for managing adult genetic disorders may not be readily available.

Fortunately, there is now a burgeoning set of web-based resources that make clinical cancer genetics much more accessible to the interested practitioner. For example, the NIH-funded website GeneTests (http://www.genetests.org) has become an indispensable tool in the kit of all clinical geneticists. It includes very lucid, up-to-date, authoritative summaries of specific syndromes, their manifestations, and diagnostic criteria. It also provides an invaluable compilation of certified laboratories that can perform CLIA-certified genetic testing for clinical decision making. It is a fabulous resource.

The website http://www.genetictools.org is part of the primary care genetics initiative that brings health-care providers to a place where they can find this kind of information very quickly. It is certain that the Web will be an essential part of solving the genetics workforce problem as time goes by, particularly on the health-care professional side where web access is practically universal. For consumers, this is a larger hurdle, since not everyone has access to the Internet. But for clinicians, these materials are increasingly available.

Turning briefly to medical genetics, the number of subspecialty certificates for M.D. clinical geneticists issued by the American Board of Medical Genetics has fallen steadily from slightly under 300 when the board was established in 1982 to around 60 in 2002 (Korf et al., 2005) (see Figure 2-2). It is discouraging that at a time when the need for genetic services is exploding, the number of trained and certified practitioners of the subspecialty of medical genetics is decreasing. This is indicative of the fact that no new programs in medical genetics have been established for quite some time, probably because only 42 percent of the approved training slots (82/193) in the existing programs are filled (see Figure 2-3).

At a 2004 watershed meeting held as part of the Banbury Conference series that addressed the issue of training physicians in medical genetics, a list was developed of reasons for declining numbers of physicians choosing medical genetics as a career. It included lack of exposure and awareness in medical school, low compensation, lack of clinical role models, poor

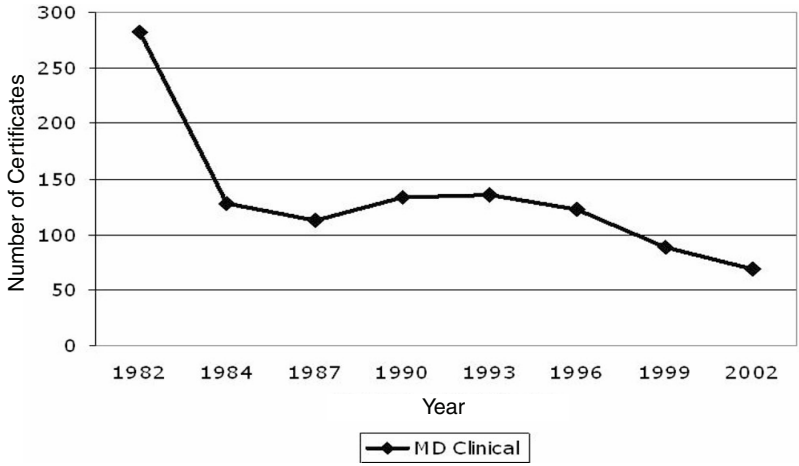

FIGURE 2-2 M.D. certificates issued by ABMG since its inception.
SOURCE: Korf et al., 2005.

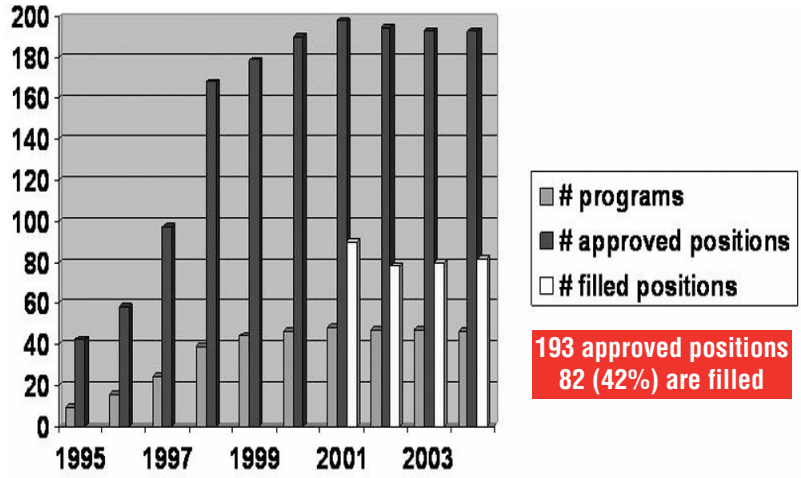

FIGURE 2-3 Genetics programs, approved and filled positions.
SOURCE: Korf et al., 2005.

reimbursement for services, and a very long training period that usually mandated certification in two specialties (Korf et al., 2005).

Proposed solutions to the dwindling numbers of medical geneticists included increased recruitment, strengthening the core training of the generalist medical geneticist community, strengthening the core training of the diverse group of health-care providers like those I listed at the beginning of my presentation, partnering medical genetics training programs with other training programs—such as combined residency programs in genetics and pediatrics, internal medicine, and maternal and fetal medicine that would reduce the total amount of time required to become certified in both. There are efforts underway to expand this list, and there are also a few joint subspecialty fellowships that are available that might help to recruit some additional candidates, but, at present, these trends do not bode well for the clinical cancer genetics workforce of the future.

From my perspective, medical oncology is one discipline in which the professional society, ASCO, has really done a spectacular job. The ASCO recognized early on that the need to provide competent clinical cancer genetics services was going to be a major issue for its membership. It embarked on a series of measures designed to remedy the genetics-related knowledge deficit that we oncologists have. Its solution began with a series of "train the trainer" courses, in which interested clinicians were brought together from around the country and taught how to teach others to understand cancer genetics. This was followed by a series of major CME events tied to its annual meeting, one of which was a 2-day course comparable to courses used to prepare for board review.

The ASCO developed position statements on genetic testing in 1996 and 2003, both of which have been very influential in guiding the evolution of this new area of interest. The first statement is the source of the oft-cited guideline that a 10 percent probability of being a mutation carrier was a sufficient basis for proceeding with genetic testing. That statement was not evidence based; it was intended as a rule of thumb or informal guideline, but it immediately became the standard of care. One of the lessons for those of us who were involved in that process is to be very careful about these kinds of position statements and guidelines. The position statements are quite comprehensive and even address topics such as reimbursement and coverage of services, regulation of testing, counseling, and confidentiality, as well as research and education.

The ASCO developed a self-education cancer genetics training module (Oncosep) and, most effectively, the cancer genetics and predisposition

curriculum slide sets, which have been a fabulous self-education and teaching resource. For those who have not seen the current version, it is really worth your time to take a look. It is only several years old, and consists of a CD-ROM and explanatory text for most of the common hereditary cancer susceptibility disorders that are likely to be encountered. It has 11 different modules including all the major site-specific syndromes and a wide variety of less common disorders, with more than 500 slides, including full-color photographs illustrating syndromic phenotypes. It is a terrific tool, and we use it all the time for teaching both professional and lay audiences.

Several weeks ago, ASCO published a major study in the *Journal of Oncology Practice* (Erikson et al., 2007), that warns of an impending crisis in medical oncology manpower over the next 15 years. This analysis indicated that the demand for oncology services in general, not just genetics, is projected to increase by 48 percent over the next 15 years as the U.S. population ages. Simultaneously, the supply of oncologists is expected to grow by only 14 percent, this combination is projected to result in unmet demand for 9.4–15 million patient visits and a deficit of clinical oncologists ranging from 2,550 to 4,080, which is between a quarter and a third of the total current oncologist workforce. The analysis was based on the assumption that there would be no change in practice patterns, service use, or cancer treatments, a highly improbable assumption.

How might this affect cancer genetic care? For better or worse, oncologists are major players in the provision of cancer genetic services. A 1999–2000 survey of 1,251 U.S. physicians in various specialties around the country, including 221 oncologists, found that among all tertiary care providers, medical oncologists had the highest rates (65 percent—compared to 30 percent for primary care physicians) of ordering a genetic test or making a referral for genetic testing in the previous year (Wideroff et al., 2003a). Of all physicians interviewed, 48 percent felt that medical oncologists were qualified to do genetic counseling. Although one could debate whether that is an accurate assessment, it seems that nononcologist practitioners are, in fact, sending patients to oncologists for genetic services. Fifty percent of the oncologists interviewed reported feeling qualified to offer genetic counseling for cancer susceptibility, and 85 percent of the oncologists felt qualified to recommend genetic testing for their patients. They were six times more likely to describe themselves in that fashion than were primary care providers (Freedman et al., 2003). In a very simple test of cancer genetics knowledge, oncologists were 2.7 to 5.7 times more accurate in their genetic information than were primary care providers (Wideroff et al., 2005).

Consequently, if the predicted shortfall in oncology services materializes, it will represent a very serious constraint upon our ability to meet the demands for these services. My own personal experience in trying to recruit clinical investigators for my intramural research program at NCI illustrates how difficult it is to find physician investigators with the appropriate training and interests. I have done four major searches for tenure-track or tenured-level investigators during the last 6 years, considered 50 candidates, found 24 unqualified, interviewed nine, and hired one person.

Robin Bennett did such a good job presenting the situation regarding genetic counselors that I do not need to discuss those providers in detail. I should bring to your attention, however, a cancer genetics subanalysis that was done as part of the NSGC's most recent (2006) professional activity survey. The NSGC reported that there were only 176 respondents (of a total membership of 1,912) who reported devoting 50 percent or more of their time to cancer genetics. A larger number (perhaps 40 percent) described themselves as seeing some cancer genetics patients. From my perspective, genetic counselors are a critical piece of the clinical cancer genetics workforce, but their numbers are far below what the demand requires.

The comment I made earlier regarding the obstetrics and pediatrics basis of medical genetics applies in the counseling arena as well. There are only a limited number of training opportunities in which genetic counseling students can be exposed to adult genetic problems. Consequently, many counselors finish their training without having had as much exposure to adult genetic disorders as one might like, especially given the direction that the field seems to be taking.

I would like to highlight one important area in which genetic counselors are, in my opinion, not being used in an optimal manner. When I came to NCI, I joined the National Society of Genetic Counselors, and I participate in their cancer interest listserv on a regular basis. Often, I observe counselors being encouraged to make medical recommendations for their clients by practitioners who themselves don't know the correct answers. In many communities, the genetic counselor may be by far the most knowledgeable genetics practitioner, but, in my opinion, it is inappropriate to expect them to assume responsibility for complex medical decisions that are beyond their formal training. My impression is that referring clinicians are placing counselors in awkward and difficult situations that may not be in the patient's best interest. Correcting the lack of cancer genetics knowledge among health-care providers would go a long way towards alleviating this problem.

I should next like to mention advanced oncology-certified nurse (OCN) practitioners. The OCN program is composed of a series of formal training levels with increasing responsibility and autonomy. There are about 22,000 OCNs nationally. They spend most of their time administering chemotherapy, but the Oncology Nursing Society has recognized that part of their role should be helping to identify patients who are at increased genetic risk of cancer and who may be in need of referral to a clinical cancer genetics professional. In addition, a growing number of OCNs are obtaining advanced training in genetics so that they may fill the role of frontline cancer genetics care providers.

There are about 1,300 advanced OCNs, for whom genetics makes up a significant part of their formal training and certification requirements. Currently, their role has been primarily that of a nurse educator. One hundred fifty advanced OCN specialists make up the next higher level of training, responsibility, and independence. Many advanced OCN specialists have a master's degree, and they are required to have completed 500 hours of advanced clinical practice. At the top of the career pyramid, one finds a group of particular interest in the current context, 380 advanced OCN nurse practitioners who are extensively trained in medical oncology. Four percent of their certification exam comprises test material on cancer screening, early detection, and genetic risk assessment, so their training is very relevant to clinical cancer genetics workforce issues. These nurses have a very strong independent practice focus, working for all intents and purposes as full-fledged medical oncologists. A small but growing number of these highly trained clinicians have elected to focus their practice on cancer genetics, after having obtained additional training in cancer risk assessment, genetic counseling, and the medical aspects of hereditary cancer susceptibility syndromes. In my opinion, they represent an underutilized resource that could be efficiently and effectively employed to bridge the gap between genetic counselors and physician-trained oncologists.

There are several other major organizations that are playing a significant role relative to improving the clinical cancer genetics workforce. The NCI's designated cancer centers represent a critical component in the developing cancer genetics care system. In 2002, NCI followed up a 1993 survey to determine how the scope and volume of genetic services provided to the 61 NCI cancer centers had changed. Forty-six of the 56 (82 percent) responding centers reported offering at least some specialty services for evaluating and managing members of cancer-prone families. This represented a 50 percent improvement over the 1993 level, but there still were

20 percent of the institutions at the highest level in the oncology care system that offered no genetic services at all. Most (91 percent) of those offering services were prepared to evaluate and manage patients suspected of having a familial cancer disorder, as well as offering risk assessment programs for persons with a rather undifferentiated history who were in need of a more general clinical risk assessment. These developments are very encouraging. Almost three-quarters (71 percent) of NCI cancer centers had a dedicated family cancer clinic, and almost all of them (91 percent) had one or more genetic counselors on staff. Interestingly, gynecologic oncologists were an important source of clinical cancer genetics care at these institutions. Approximately one-third of the centers were seeing more than 300 high-risk patients a year, so there is a reasonable level of clinical activity occurring at the tertiary referral center level within the U.S. health-care system. It is particularly encouraging that in every genetics service category covered by the survey, the proportion of centers providing those services was greater in 2002 than in 1993 (Epplein et al., 2005). The fact that a significant and growing volume of clinical cancer genetics services are being provided at these institutions represents an important advance in our ability to meet the increasing demand for these services. Of course, many major cities in the United States do not have an NCI-designated cancer center, but these institutions are increasingly providing outreach and satellite services to geographically nearby communities as you will hear described by Dr. Weitzel in his presentation.

The National Comprehensive Cancer Network (NCCN), which began with the goal of developing comprehensive guidelines for the diagnosis, treatment, and supportive care of cancer patients, is an unheralded source of positive influence on clinical cancer genetics. Without much fanfare, NCCN has expanded its evidence-based guideline development to include cancer prevention, detection, and risk reduction related to persons at high familial or hereditary risk. In fact, this organization was the first to recommend that MRI should be a routine part of breast cancer screening of high-risk women. This online set of evaluation and treatment algorithms is used by clinicians around the country who are increasingly aware of the availability of management guidelines on the NCCN website for various genetic syndromes such as hereditary breast/ovarian cancer and hereditary colorectal cancer (http://www.ncc.org/professionals/physician_gls/default.asp). This information has the potential for exerting a major influence on practice behavior relative to cancer genetics. The algorithms walk you step by step through the process of assessing and developing a management

plan for persons at increased genetic risk of malignancy. These tools make it possible for providers who do not have formal training in cancer genetics to do a solid job of caring for these patients.

The National Coalition for Health Professional Education in Genetics has been a major mover in this area. It has developed core competencies in genetics that are actively promoted for all health professionals, so that health professionals appreciate the limitations of their genetics knowledge, understand the psychosocial implications of genetic services, and know how and when to make genetics referrals (http://www.nchpeg.org/). The Internet already contains a tremendous amount of readily accessible cancer genetics information that can facilitate practitioners responding to the need for these services in a well-informed, evidence-based fashion. And what is on the Internet now is only the tip of the iceberg. It is critical for clinicians who encounter familial and hereditary cancer syndromes in the course of their daily practice to familiarize themselves with the resources that are available. One excellent starting point is NCI's PDQ Cancer Genetics website (http://www.cancer.gov/cancertopics/prevention-genetics-causes/genetics), which contains up-to-date summaries of various broad topics, cancer site-specific modules related to the more common cancer susceptibility syndromes, and links to a wide variety of additional resources that can aid in providing first-rate care to patients at familial or genetic risk of cancer.

Finally, let me mention the role of the public related to cancer genetic services. In a study exploring factors associated with differential awareness of genetic tests for increased cancer risk, 27,405 respondents from the 2000 National Health Interview Survey were asked if they had ever heard of genetic testing. At that time, 44 percent said yes: 50 percent of white respondents, 33 percent of African Americans, 32 percent of American Indians/Alaskan Natives, 28 percent of Asian/Pacific Islanders, and 21 percent of Hispanics. Test awareness was significantly associated with higher education, white race, age less than 60 years, and private health insurance, indicating that targeted strategies to ensure risk-appropriate utilization of genetic counseling and testing might be beneficial (Wideroff et al., 2003b). From my perspective, it is not unreasonable to expect our patients to play a role in this whole process. At the very least, they bear some level of responsibility for keeping track of their family history and bringing that information to the attention of their health-care providers. As in all other areas of medicine, patients who can serve as their own advocates are likely to fare better in obtaining the services they need, so it is incumbent upon us to bring these issues and resources to the attention of the general public.

Several of this morning's speakers have already alluded to the surgeon general's family history initiative. Everyone is supposed to sit at the table at Thanksgiving and take a family history (http://www.hhs.gov/familyhistory/). We are all being encouraged to take advantage of family gatherings, such as Thanksgiving, to familiarize one another with our family's medical history, and there are a variety of tools online to facilitate doing so. A good example is the CDC's family history project (see http://www.cdc.gov/genomics/public/famhistMain.htm). The CDC is currently developing a web-based family history tool for practitioners that will soon be coming to a computer terminal near you.

There are a number of computer-based cancer risk-assessment tools from academic and other sources designed for use by laypersons, that are readily available on the Internet. Five of them have been evaluated recently (Kelly and Sweet, 2007). Some concerns about these tools have been expressed, including unavailability to the poor and less literate, limitation to a few cancer sites, and not having been crafted to induce desired behavior, among others. Some of these programs are designed to estimate the probability of a specific cancer developing in an individual possessing specific characteristics, while others are intended to estimate the probability that the respondent is a carrier of a specific cancer susceptibility gene mutation. These tools are readily available for malignant melanoma as well as breast, ovarian, and colorectal cancer. However, the area of risk assessment tools is in its infancy; it is certain that they will increase in sophistication, flexibility, usability, and accuracy over the coming years.

This brief overview of issues related to the clinical cancer genetics workforce would not be complete without mentioning the potential role of telemedicine in helping to provide these services. It represents one potential solution to the workforce issues that we face, particularly related to the geographic maldistribution of genetics service providers. There is a growing literature suggesting that genetic risk assessment and genetic counseling can be done in a telemedicine framework. There are several studies that have compared face-to-face counseling with telemedicine counseling and have concluded that there are no clear differences in the quality of counseling or results. Both groups of patients reported high levels of satisfaction, increased knowledge, and decreased anxiety (Coelho et al., 2005). Studies to date are relatively small, but this experience has been encouraging, and I suspect this technology will come to play an increasingly large role in the provision of cancer genetics services.

In summary, there is bad news and good news when contemplating the clinical cancer genetics workforce. The bad news is that there appear to be major shortages in both the medical genetics and medical oncology workforce related to clinical cancer genetics. The development of the current "system" of care has been haphazard and opportunistic, as providers with an interest in this problem self-select practices that target patients with these disorders. It is not widely appreciated that medical oncologists are providing a major portion of the cancer genetics care in the United States at present. If recent projections regarding a shortage of medical oncologists prove accurate, we face a growing gap between the number of providers and the demand for genetic services. I find it particularly disturbing that, in this postgenomic era that holds forth the promise of personalized medical care based on genetic profiling, genetic counseling as a discipline is not growing as rapidly as it should. You have heard some of the reasons from Ms. Bennett. From my perspective, one of the major weaknesses in genetic counseling training programs (as well as in medical genetics training programs) is the lack of formal exposure to adult genetic disorders, which is where the future demand is likely to be greatest. It is frustratingly difficult to get this information into training program curricula, and perhaps even more importantly, into the licensing and certification examinations. If knowledge of genetic principles were an integral part of these high-stakes examinations, genetic material would of necessity be integrated into training program curricula. But those who formulate and write the examinations do not include questions on material that is not part of the training curriculum. This is a vicious circle that is exceedingly difficult to break.

On the other hand, the good news is that the genetic revolution is here, and we are already beginning to see the fruits of this progress. There is no question that the need to enhance the genetic knowledge base for those who are involved in genetic services has been recognized. The professional societies and a variety of other interest groups have engaged in serious efforts to correct these problems, and significant progress has been made in upgrading the genetics knowledge base accessible to and commanded by diverse classes of health-care providers. Of course, much remains to be done. The structural issues in both education and health-care delivery have been recognized, but the progress toward solving those problems has been slow.

Personally, I also find it very encouraging that such a broad range of disciplines is committed to helping this group of patients. That can only be a good sign, especially since there is a trend towards a multidisciplinary team

approach to providing clinical cancer genetics services. It cannot be said often enough that an adequate family history is an essential first step in the cancer risk assessment enterprise, and, fortunately, there are multiple efforts underway now to encourage and facilitate practitioners taking an adequate family history and teaching patients how to take their own family history and build a pedigree. Computer-based technology, for example, web-based resources and telemedicine, has the potential to mitigate these problems; steady progress is being made in this realm.

Finally, we must find a way to increase the supply of health-care providers with an interest in and the knowledge required for genetic risk assessment and management. The genetic counseling career path needs to be enhanced to provide opportunities for advancement and to both attract larger numbers of students and retain a larger proportion of those who are formally trained. I believe that advanced oncology nurse practitioners are an underutilized resource in the world of cancer risk assessment. My sense and personal experience are that they are a cost-effective hybrid of genetic counseling and medical oncology, one that may be ideally suited to mitigating the workforce shortfall that appears to lie ahead. They have the clinical skills that genetic counselors do not possess and can function as medical decision makers as a result of their training, licensure, and certification. They lack the counseling skills that make up the strength of genetic counselors, but there are training opportunities for nurse practitioners to remedy this deficiency. A thoughtful, systematic, organized approach to solving the workforce shortfall is required to meet these challenges. I hope that the insights and ideas generated by today's workshop will represent an important step in that direction.

Dr. Weitzel: Delivery and Research Issues: Providing Community-Based Services: I am going to talk about one cancer genetics practitioner's efforts to integrate aspects of health services delivery as well as workforce-related issues. I am going to give a background perspective on why interdisciplinary training is critical for this science and suggest that cancer genetics is an interdisciplinary specialty, and then I'll talk about how we might go forward.

At the City of Hope National Medical Center, I have four full-time cancer risk counselors in my program. I use both nurses and advanced practice nurses and genetic counselors. I work with the International Society of Nurses in Genetics. They are a small organization that has been doing

credentialing and encouraging the incorporation of genetics in nursing since before the American Board of Genetic Counseling was established. I also have research associates to help me link the clinic and the research enterprise.

Why is a program in genetics dedicated to cancer risk essential, and how do we leverage comprehensive cancer center expertise to elevate the quality of care in the community and promote a multidisciplinary care model? I very much come from the medical model, and I feel that it should be a multidisciplinary model.

One of the reasons creating such a program is such a challenge is because, if for example, we see a 59-year-old woman with breast cancer, and her daughter, 29, has had a preventive mastectomy, will her granddaughter be spared? We are dealing with both the risk reduction options being in some cases quite draconian, as well as the fact that there is an emotional burden in these families, making counseling essential to help them work through these processes. It is not just a genetic test, it is a whole process.

Cancer is a complex disorder. Complex issues arise in genetic predisposition testing. Proficiency in cancer risk assessment requires cross-disciplinary expertise. These premises arise from our perspectives as trained medical oncologists and then as trained geneticists. The predisposition testing process requires more steps and provider time than many other clinical tests. That is going to make it a practice model with major economic barriers to feasibility. It is just not feasible as an economically rewarding or even neutral practice model, yet we need that quality of care. So I am going to highlight from the cancer center perspective why it has to be a marquee service and value-added part of comprehensive care, though it probably will never be self-sufficient and stand alone economically, yet it must be integrated in so many systems.

Cancer risk assessment involves the state of the science, the state of the patient's previous cancer experience, the state of the technology, the state of the art in terms of management, and the state and federal statutes on genetic discrimination. The genetics knowledge base is exploding from Drs. Fraumeni and Li observing the connection between P53 and a cancer syndrome a number of years ago to today's more than 40 different syndromes with a genetic basis and tests, many of which are in common use in the clinic. Our patients come in with a special state of mind and previous cancer experience, and you do need to understand that. The oncology nurses bring that to the table, because they know about death and dying and

cancer care, palliative care, and the burden that puts on people. I think that the counselors have experience in counseling people through the genetic legacy issues, so I think that is an important aspect.

The state of the art in terms of management is evolving, as was already pointed out. In the 10 years since BRCA testing became available, I have seen a sea change in evidence supporting intervention, taking it from a research-based practice, as Dr. Ganz pointed out, to a clinical practice with evidence-based interventions, and in some cases, interventions that preceded the evidence for the general population application. Colonoscopy and HNPCC is a good example, where the evidence for efficacy in down-staging and reducing mortality in our patients preceded the kind of evidence we obtain from big population studies.

The issue is, do you want to know your risk for cancer, and how do you structure cancer risk counseling clinics? How do you quantify cancer risk? There are empiric cancer risk models that rely on population studies, as well as ways of estimating the probability of a mutation. There is genetic testing and gene-specific risk estimation. A cancer risk counseling program should take the patient that Dr. Ganz described earlier, and even though the testing was not informative to begin with, appropriately assign her to high-risk screening because her empiric risk by the Elizabeth Claus risk model was over 30 percent, based on having two first-degree relatives with breast cancer under 50. We would have classified that individual as having a high risk or moderate to high risk based on that alone, and appropriately Dr. Ganz and her colleagues did the same until they ultimately got informative testing. It shows that just knowing how to perform a genetic test is not enough. You need to know the empiric risk guidelines.

The other reason I mention that is, if you look at the standard referral guidelines, the yield on BRCA testing is around 20 percent. In other words, if we are getting the right referral population, we only get 20 percent of our cases positive. That means 80 percent of the patients have uninformative testing and need empiric risk assessment. So we have to be more adept to address these problems in both ways.

Cancer risks are more specific when gene testing is informative.[1] A group of 491 women with stage I or II breast cancer and a BRCA-1 or -2

[1]A negative test will be interpreted differently depending on whether there is a known mutation in a family. If a family member tests negative for the known mutation, it is unlikely they have increased susceptibility for cancer. They may or may not get cancer, but are presumably average risk. The test result is informative, or a true negative. Members of a family without a known mutation who test negative have an uninformative result (or false negative)

mutation in the family were followed to contralateral mastectomy, breast cancer, death, or last follow-up (Metcalfe et al., 2004). Actuarial risk of contralateral breast cancer was 29.5 percent at 10 years. But there were factors predictive of reduced risk: BRCA-2 vs. BRCA-1 mutation, age 50 or older at first diagnosis, use of tamoxifen, among others. The idea was, not only is risk estimation relevant for the first time you get cancer, but there are risks to survivors, the risk of second or new primary cancers in genetically predisposed individuals. This is a problem across the board.

Many people come in because they are concerned about legacy. I am reminded of Betty Ferrell and Marcia Grant's work on quality of life in City of Hope, where one of the number-one concerns of women surviving breast cancer was, what is my daughter's risk? So these legacy issues often bring the patient to the clinic, but the reality is, they don't realize that they should be there for themselves, because of the second primary cancer risk.

These data also point out that there are potential interventions. As I mentioned, hormonal modulation by oophorectomy or tamoxifen reduces the risk of a second primary cancer, so we already have insights. What is really striking is that if you don't recognize this syndrome, the risk of ovarian cancer, even though it has not been seen in the family before, is substantial, and ovarian cancer was the cause of death in 25 percent of the stage I breast cancer patients in this series (Metcalfe et al., 2005).

There is medical liability if we don't recognize the syndrome. Failure to diagnose is going to be an issue in this field. We are pressed to have an adequate workforce to provide the care, while at the same time recognizing that we are being expected to have the knowledge and the ability to deal with these complexities. My tenets are basically that there is a documented efficacy of intervention that makes it medically necessary care that is covered by insurance and is cost-effective in families. We have reason to go forward and to integrate this into practice. Because of the new primary cancer risk issue that Dr. Ganz already alluded to in discussing the idea of surgical decision making, patients are now facing the concept of both treatment consultation and decision, as well as concurrent prevention issues.

As Yogi Berra said, "Predictions are risky, especially about the future." We are trying to predict a likelihood, so the risk models have to be

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that does not provide information about any possible mutation that was not detected in the family of the family member. Also called uninformative are negative tests on probands, individuals, affected or not, testing negative from families with cancer whose members have not been tested, and those with variants of uncertain significance, and the like.

improved. We have to be able to have some confidence intervals that are relatively narrow around our predictions. In our own program, I don't think of precise numbers. When you hear 87.5 percent, or you run the Gail model and you get a 2.35 estimate of risk in the next 5 years, how did they get to the second digit? I have no idea. My point is that we try to classify them into high, moderate, or average risk, because nobody has no risk. People who are not as adept at counseling forget to say that just because you don't carry the familial mutation doesn't mean that you are not going to get cancer. Figure 2-4 displays our lifetime risk model.

Most of the patients I take care of fit into the moderate category, because we do not have informative testing so often. But the good news is that we have reasonable guidelines now under each category. You will notice in Figure 2-4, I have breast MRI under the moderate risk, but really at the high end of the moderate, because we are just trying to describe what might be reasonable in a generic way for most women. So, there is a sliding scale under moderate. The person that Dr. Ganz described had a high enough risk to warrant the MRI and other things if necessary, but others who have one first-degree relative do not. You have to tailor the approach to individuals. We have added the second primary risks for breast and ovarian cancer, so this is our attempt to try to stratify risk.

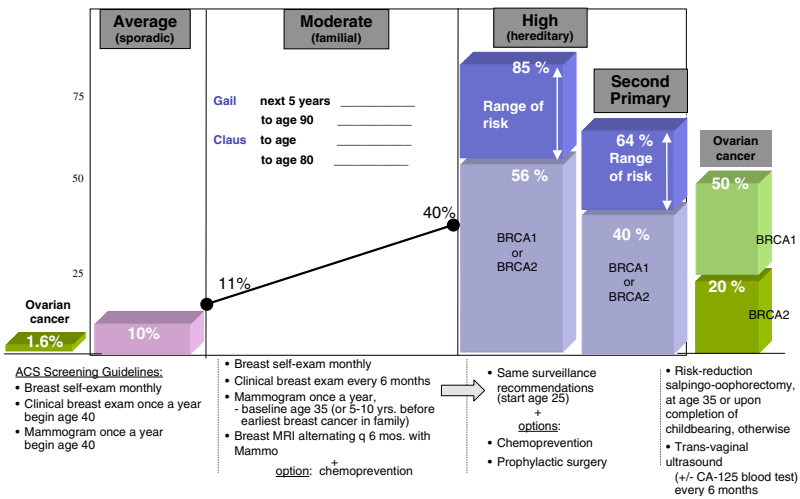

FIGURE 2-4 Lifetime risk for breast or ovarian cancer.
SOURCE: City of Hope Cancer Screening and Prevention Program Network.

In our own Department of Clinical Cancer Genetics program, we have a two-pronged approach. This illustrates how, at a cancer center, we approached the issues in cancer genetic counseling for the center and the community. We have a research support core and a clinical cancer genetics laboratory. We have both the cancer screening and prevention program network that I am going to describe for you at some length, and we created a cancer genetics education program that is supported by an R25E cancer education grant; that became significant for us in terms of our health services research and also in changing peoples' behavior.

Our own program is classic, in the sense that we are doing analysis of personal risk factors and pedigrees to identify individuals and families at risk and medical planning using surveillance, prophylaxis, and prevention. We provide genetic testing and counseling and psychosocial testing and support. Finally, I share Dr. Greene's sense of the importance of not losing opportunities for research. Because most care is delivered in the community, if we cannot effectively follow rare cancer families, the ones that have mutations, we will not be able to develop the next level of interventions and understanding. We foster interdisciplinary clinical, epidemiological, and cancer control studies, and I have been thinking about how we can bring the center's clinic and the community together.

We consider the clinic to be our community laboratory. We connect to health services research, underserved and multiethnic populations research, biobehavioral research, and chemoprevention trials. I link my clinic to our chemoprevention trials, clinical outcomes research, and we collaborate with extramural groups. I have displayed these relationships in Figure 2-5. That is our cancer center approach (MacDonald et al., 2006).

How does one get out into the community? Because I was asked to talk about how we became involved in community care, I am going to describe how we developed our clinical network and the activities that the network stimulated. When I first started at the City of Hope in 1996, we set up our center program. Then, an oncologist in Santa Barbara told us he had no genetic counselor, and he recognized that that kind of care was necessary. Could we help? We set up a contract to provide our advanced practice nurse there 2 days a month to see all the cases for the community. It is a foundation-supported activity. The patients then come down to see me once for a results discussion. Most of the preliminary work has been done, so when the patients come down it is for only one shorter visit instead of two longer ones. They save themselves one of two 2-hour drives.

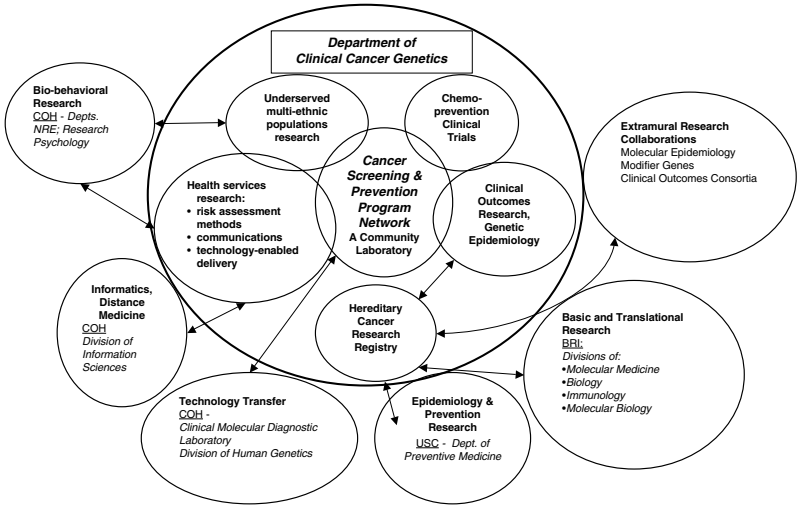

FIGURE 2-5 Interdisciplinary research resources and relationships.

At the same time we set up a similar clinic in Fullerton, which I attend 2 days a month with my genetics nurse. These arrangements caused us to think about serving our City of Hope bone marrow transplant unit in Phoenix as a result of a request from there. I recruited a genetics nurse there, and I run the program with her via telemedicine. Telemedicine was mentioned already by Dr. Greene as having real potential for delivering counseling services of good quality, and we used it here for practice development.

Next, we received a grant from the state of California to do outreach to underserved populations, and we began a demonstration clinic project associated with Olive View Medical Center, which is the county hospital in San Fernando Valley, and Queen's Care Health and Faith Partnership, which is a faith-based initiative providing care for people at the 200 percent or less poverty level in North Hollywood and surrounding areas. Basically, Tenet Health Care Corporation bought out a local hospital and had to set up a community foundation that we then partnered with.

We set up two demonstration clinics. We did a needs assessment survey showing that our predominantly Latino cohort was interested in preventive

care, despite their economic burdens and their inability to meet standard needs (Ricker et al., 2007). Then the question was, if we build the clinic, will they come, and, more importantly from a clinician's perspective, will they use it? We went on to demonstrate that in our cohort of 119 predominantly Latina patients, we had 88 percent keeping their appointments to my clinic, a stunning result that is better than my cancer counseling clinic at City of Hope (Ricker et al., 2006). At follow-up at 1 year we still had 77 percent (72 of 94 eligible patients) completing follow-up surveys.

What was very gratifying to me in this group with very few resources, many of them either on Medi-Cal or uninsured, is that after counseling an increased number of patients received clinical breast exams (from 81 to 91 percent), as well as mammograms (from 75 to 82 percent). We are helping them try to increase resources in the community, but the fact is that they came, they learned, and they are coming for appropriate care. Because our grant ended, I am not paid to see these patients, so we had a telemedicine unit installed, and I see the patients that way with the counselor there on site. I also see them again for the second visit through telemedicine. I do not bill for it because in an urban setting telemedicine is not reimbursed. It is only reimbursed if you have a certain "rurality" quotient.

We received a state grant to set up telemedicine in Redding and Madera in California. It turns out Redding wouldn't qualify for telemedicine reimbursement from CMS because it has 150,000 people. The surgeon there told me no one was offering genetic counseling in Redding, and he needed help to integrate this into his breast cancer practice. We trained his nurse in counseling sufficiently to set him up with a telemedicine unit, and he can then present his cases to us. That got us thinking about network modeling. We now have a practice development network at St. Joseph's in Orange, at Mission Hospital in Mission Viejo, and most recently in Boise, Idaho. We have set up telemedicine-supported networks, so communities can develop genetic care in their own community center but come to us for advanced practice help.

How do we build our cancer screening and prevention program network? We provide professional (skills for the cancer risk counselor) and lay (awareness for the community and appropriate referrals) education on site at these individual locations. We provide a site survey and needs assessment to help them figure how to set up the clinics in the setting. Staffing, administrative support, clinic family counseling room, phlebotomy capacity—all these are relevant issues. Because BRCA testing often is not run through the hospital because of the billing issues I mentioned earlier, the question

of how phlebotomy is paid for, since it can't be billed without a test associated with it, needs to be dealt with. There are many logistical things to deal with in setting up clinics.

We provide the professionals with common data forms, clinic questionnaires, family history forms and things they need to get started, and we help them to establish the services. They pay a monthly subscription fee to City of Hope for my medical management time and direction. Then we hope they can participate in our hereditary cancer registry; we want the community to participate in research, especially for things such as the cooperative family registries. These are all opportunities for us to learn from these families in the community setting.

From 2001 to 2005, the program at St. Joseph's Hospital of Orange grew from 45 to 208 referrals, and with my help they justified to their administration another full-time equivalent (FTE) position in genetic counseling. They have also gone on to do economic modeling of the side benefits to the hospital of running their program. These include greater MRI revenue, risk-reduction surgeries, and additional screening revenue. These patients come to the clinic, and they bring their family members who may be coming to the hospital system for the first time. Even though they might not be conversant with economic medicine, we try to give them every tool to justify the services on a revenue basis.

How do we bridge the gap in terms of quality? Using telemedicine, we have been looking at different health services delivery issues—from genetic risk assessment with a counselor alone, initial risk assessment with a counselor and a follow-up visit with a doctor, initial visit and follow up with the genetics team, or genetics counseling and risk assessment through teleconferencing. We are examining models to try to define a research project well enough to obtain funding by the AHRQ or other sponsors.

We have a weekly working group that reviews about 35 cases every week. Anybody in the network can present a case to our multidisciplinary working group. We help them then develop their strategies for risk assessment and offer recommendations for surveillance and risk management. We can improve the quality of genetics care in the community in this way using our team for those community programs that couldn't afford to hire me and the team separately. At the same time, we have the opportunity to inform them of, and encourage them to participate in, our research. Everybody who comes into our clinics, whatever his or her risk, is offered involvement in my registry, and we look for different opportunities for research for each.

What has been the effect of working group participation on community center quality? In a 1-month survey of situations where people came to our group either through telemedicine or by actually coming to the meeting, we advised redirected diagnostic evaluations or workup strategies in eight of the cases; identified best genetic testing candidates in a family, such as testing the youngest; interpreted or clarified genetic test results (how they interpreted the importance of variants of uncertain significance); augmented risk assessments; identified candidates for studies; and provided a consensus on risk assessment management for a total of 35 instances affecting multiple quality elements in each case. We provided that next level of quality in the community setting by allowing them to come into a standard case-review-like setting, but through a variety of technology-enabled mechanisms.

Then we link these patients to our prevention trials. We have a collaborative trial with Dr. Malcolm Pike at the University of Southern California (USC) Department of Preventive Medicine and others using a gonadotrophin-releasing hormone (GNRH) agonist to reduce breast density while preventing the consequences of menopause (Weitzel et al., 2007). We give a low dose of estrogen as partial replacement after using the GNRH agonist to turn the ovaries off. We saw a 30 percent reduction in breast density over a 1-year trial in BRCA-1 carriers between 20 and 40 years old. Of my published cohorts, I was able to get three of the patients from our underserved cohort. I am enhancing our minority accrual by our community outreach, and the patients are able to participate in a prevention study that they would not normally have had access to.

I want to describe our registry a little bit more because it is a really important partnership. We comply with the provisions of the HIPAA Privacy Rule. We get authorization from the patients for use of their health information. We draw a one-time sample of blood that is processed into a variety of useful biospecimens. And, most important, we get authorization to recontact the patients, enabling us to carry out prospective follow-up from the time that we see them in the clinic. We understand that we are limited to some extent from an epidemiological standpoint because the selection of our cohort is clinic based rather than general population based, but at least we are doing the best we can, and I think we are gathering useful information. Very few of the patients who come to the clinic refuse to participate; we have about a 97 percent uptake on the protocol.

What does our registry show us? Table 2-1 displays the characteristics of the hereditary cancer registry dataset, and Table 2-2 shows some of the

TABLE 2-1 Characteristics of the Hereditary Cancer Registry Dataset

	N
Type of Cancer*	
Breast Cancer	997
Ovarian Cancer	98
Peritoneal	8
Colorectal Cancer	114
Uterine Cancer	35
Melanoma	32
Other	192
Unaffected	672
Type of Sample	
Blood/DNA	2,271
Lymphocytes	2,250
Plasma	443
Serum	40
Ethnicity	
Caucasian	1,568
Hispanic	257
Asian	93
More than One Race	70
Other	47
African American	25
American Indian or Alaska Native	9
Native Hawaiian or other Pacific Islander	2

NOTE: Including multigenerational pedigree and clinical data on 2,071 participants.
*Column totals may exceed 100% due to >1 cancer type in some individuals.

results. The majority of our cancer patients have breast cancer, but the numbers of our colon cancer patients are increasing. The kinds of biospecimens we have collected are displayed at the bottom left of Table 2-1, with blood and DNA for over 2,000 individuals. We emphasize plasma, which we started collecting when proteomics became relevant.

Part of the registry I have been doing without grant funding, so I have had to be conservative. We chose plasma because I am collecting for DNA anyway, and I can spin the sample down. The investigators doing mass spectroscopy for proteomics tell me that plasma will work as well as serum. Our ethnicity is predominantly Caucasian, as it is for most high-risk clinics, but we also are picking up a reasonably good-sized Hispanic population, and that has doubled in just the last 2 years.

Table 2-2 displays the 2006 BRCA testing results for our single center plus our network. We now follow over 300 individuals with BRCA mutations, and we have now tested 1,500 instead of 1,000 individuals. Therefore, we have a large cohort of people for follow-up studies. These data have enabled participation in multi-institution consortia that are essential for these rare conditions. As a result, with many other research groups, we have been able to publish on the striking concordance in receptor status in bilateral breast cancers in BRCA carriers (Weitzel et al., 2005a). Our work in the underserved clinic has allowed us to publish on the prevalence of BRCA mutations in other ethnic and racial groups, such as the cases of Hispanics with mutations and founder effect in high-risk families belonging

TABLE 2-2 Registry BRCA Mutation Status and Cancer History of Probands as of May 2006

	Mutation Status		
	Positive	Negative	Variant
Total no. (%) N=1,097	202 (18.4%)	801 (73.0%)	94 (8.6%)
Gender			
Female (n=1,078)	198	786	94
Male (n=19)	4	15	0
Affected	170 (84.2%)	599 (74.8%)	70 (74.5%)
No. with breast cancer	104[c]	502[d]	59
No. with bilateral breast cancer	35	45	7
No. with ovarian cancer[a]	17	41	2
No. with breast and ovarian cancer[a]	14	11	2
Average age at first breast cancer diagnosis	40.7	43.8	41.0
Unaffected	32 (15.8%)	202 (25.2%)	24 (25.5%)
Race/Ethnicity			
Caucasian	145 (71.8%)	600 (75.0%)	50 (53.2%)
Latino	36 (17.8%)	96 (11.9%)	12 (12.8%)
African American	3 (1.4%)	4 (0.5%)	6 (6.4%)
Asian/Pacific Islander	9 (4.5%)	44 (5.5%)	16 (17.0%)
Other	0	7 (0.9%)	1 (1.1%)
Mixed[b]	9 (4.5%)	50 (6.2%)	9 (9.5%)

[a]Includes Fallopian Tube and Primary Peritoneal.
[b]Combination of above and/or non-Latino.
[c]One male.
[d]Six males.

to that ethnic group (Weitzel et al., 2005b), which may have implications for prevention.

We also have been able to publish with many groups on various reproductive factors and the risk of breast cancer in BRCA mutation carriers showing significant reductions in risk for those with later menarche, longer breast-feeding and early oophorectomy in BRCA-1 carriers and for those with increasing parity in BRCA-2 carriers. All of these studies were in the same cohort, to which we contributed probably about a tenth of the subjects.

How did we learn cancer genetics practice in the past? Through self-directed studies, hands-on experience, and reviewing the literature. I am one of the few who actually completed a genetics fellowship on top of oncology. I have decided I would not do it again, because, as an oncologist, I do not need to have a genetic certification. What about resources now available in the community? Now we have a more robust literature: the ACS national conferences on cancer genetics, the ASCO curriculum and courses, the National Society of Genetic Counselors educational material, the Oncology Nursing Society and International Society for Nurses in Genetics material, and the educational material of the National Coalition for Health Professional Education.

In our own program, we put together a number of educational components to create our cancer genetics education program with three goals in mind. First, I have my R-25T-funded program to create the next generation of program leaders in cancer genetics research. Candidates, oncologists or geneticists, spend 2 years and get a masters degree in epidemiology from USC while working with us in cancer genetics. My response to questioning whether a fellowship was right for me was to develop the R-25T program.

To take it to the community level, I received an R-25E grant and a Maternal and Child Health Bureau grant using Title V funds to teach community physicians about cancer genetics. Our goal is screening level competence. Then we received an R-25E to present cancer genetics in a community-based research course, what we call our intensive course. It is a 70-credit hour course to try and create practitioner-level competence. The idea, as pilot tested with a grant from the state, was to show that we could train counselors, nurses, and physicians to work together as teams and show increments in their practice and knowledge. The basic idea is to take multiple disciplines, masters-level counselors, advanced practice nurses, and community physicians, and bring them together for training. We purposely mix them because they bring different things to the table.

With a CME/CEU-accredited 70-hour course, the goal is to promote increased access to competent cancer genetics risk assessment services in the community and to encourage community-based research participation. Some of the modules involve institutional review board (IRB) protection, how to get through an IRB at your local hospital, how to participate in community-based research, and what are the database issues that you have to deal with for funding. Our 2007 class comes from about 20 different states, and we feel we are reaching many communities, trying to seed the high quality practices in different areas. We know from evaluating results that participants in the training show increased knowledge scores and report increased professional self-efficacy and numbers of patients seen (Blazer et al., 2005).

How do we pay for all this good work? That is the real challenge. Most of it comes from various sources of grant support, primarily leveraged education grants. I am eternally grateful to the R-25E program, because I have been able to leverage a lot of these grants to build our programs and address the health services research model on the back of the education. I think education can do more than just teach people something. We also leverage philanthropic support. Genetics is pretty "sexy," so most places should be able to find someone who wants to create a legacy and give some support for a counseling program. We help to counsel people about this. City of Hope, of course, is a master of philanthropy as well, so we are coming from that mold, and we understand the power of philanthropy.

Why would another institution want to pay a comprehensive cancer center to help them create a network like this? A lot of it has to do with quality and the ability to have a marquee service. I would highlight the role of community outreach in helping my cancer center achieve comprehensive status. They have been willing to support my work, partly because it helps them achieve comprehensiveness and community outreach.

I should acknowledge the grant funding mechanisms. They were incredibly important in assisting me to translate some of these ideas into practice. Different grants that I had over time and the number of people reached include our Maternal and Child Health Bureau grant to educate about 2,800 community practitioners. We ran 10 full-day conferences for nearly 150 doctors and nurses each time. This is very much like the ASCO effort. Then most recently, we offered our intensive course and our fellowship training. We have had RO3s (epidemiologic and ELSI sections) grants, state cancer research programs, foundation and General Clinical Research Center grants, and R-25 grants.

We do it because it is the right thing to do for family health; it is a marquee program that has value added aspects, and it provides downstream revenue from the community and the potential for cutting-edge therapies. I have tried to emphasize the concept of the multidisciplinary model, the importance of education and training, cross-training, and I hope I have been able to draw together a couple of the themes of the other speakers this morning, from telemedicine to workforce-related issues.

Dr. Ferrell: I was sitting here this morning thinking about all the things that have come from this group, from the forum and IOM projects, that have been successful and moved things forward, things like the end-of-life or survivorship report and the biomarkers project, that have been able to capture the urgency of the problems. When we say "There are 10 million cancer survivors, and they have psychosocial issues and unresolved symptoms; 500,000 cancer patients dying each year, most of them in pain," there is an urgency.

We have to provide urgency to this message when it leaves this room today. We have to get at why genetic testing and counseling is critical. It is about early detection, it is about really getting to the at-risk population. The issue this morning about lack of attention to the underserved is huge. I just want to make sure that the proceedings from today send the message of the life-saving importance of these services that we want to take to the broad community.

Dr. Weitzel: If I could amplify that in the context of the underserved: the problem with the hereditary cancers is that the risk is at such a young age outside of any of the standard screening guidelines. In our underserved cohort, what was striking is that the median breast cancer size for the young Latinas that were being referred was 6 centimeters. That is obviously horrendous. If I determine who among their siblings is at risk, I can change that statistic and downstage their cancers through early detection with just mammograms and clinical breast exam without having to wait for transgenerational evidence. Not only is this life saving, but it is cost effective and justifies the expense of making these analyses.

Dr. Chanita Hughes-Halbert, Associate Professor, Department of Psychiatry and Abramson Cancer Center, University of Pennsylvania: I want to congratulate you on the extensive efforts and the success that you have had reaching out to community hospitals. I wanted to learn more

about how you did that because, as I will discuss in just a moment, it can be a time-intensive, labor-intensive process.

Dr. Weitzel: You are absolutely right, it is a time- and labor-intensive process. I started with educational outreach by holding our community forums. I did 150 grand rounds lectures around Los Angeles alone over a several year period. And because I had support from my R-25E grant, I was given the time to do that. So it all revolved around education. This created awareness in the community and an interest in delivering a good quality service. I always emphasize the pitfalls of being uninformed, so the community would recognize that, and come to me for consultation. I did not have to go to them and say "Do you want to open up a program?" They came to us after recognizing through education that there was a quality issue and that the proper training and qualifications were not there in their own setting.

Dr. Hughes-Halbert: Delivery and Research Issues: Reaching Underserved Groups: For the past 6 years, since I came to the University of Pennsylvania in 2001, I have been working to establish a clinical genetic counseling and testing research program for African American women. Why focus on African American women? I am sure everyone is aware of the disparities in breast cancer morbidity and mortality that exist among African American women in the general population.

There has been an interest in understanding hereditary breast cancer among African American women. Several studies have shown that 16 to 28 percent of these women who have a personal and family history of breast cancer that is suggestive of hereditary disease carry BRCA-1 or BRCA-2 mutations. This prevalence is similar to that observed among white women who do not have an Ashkenazi Jewish ancestry. Breast cancer is the most common form of cancer in African American women; they also have higher mortality from breast cancer than Caucasian women. So this is a population that is important.

To the extent that information about one's risk of developing disease motivates early detection and screening, genetic counseling and testing may be an effective way to encourage earlier screening among African American women who have a family history of breast cancer that is suggestive of a hereditary condition. This underscores the importance of targeting genetic counseling to African American women. Although there have been more recent efforts to try to disseminate genetic counseling interventions to African Americans, we published a review in 2004 that demonstrated

that this process isn't very effective (Hughes et al., 2004). For example, we reported research participation of whites, blacks, and other nonwhite ethnic groups in a variety of different settings in which hereditary breast cancer research was being conducted. Of 1,311 people recruited from a standard high-risk clinic, only 1.1 percent were African American and 0.5 percent other nonwhite minorities.

We are currently investigating how we can increase access to genetic counseling and testing among African American women. We have generated several key research questions that our group at the University of Pennsylvania has been addressing. How can we increase access to genetic counseling and testing in clinic-based samples among African Americans? We are also interested in understanding the most effective methods for communicating risk information and the impact of testing and counseling on African American women. Through a genetic counseling research program called With Our Voices, which is funded by the Department of Defense, we have been looking at the effect of genetic counseling and testing that is tailored to cultural beliefs and values such as those related to religion and spirituality versus standard genetic counseling.

I want to talk about our experiences recruiting women into this process. This is an issue related to access; programs with a research component might experience low participation because of concerns about participating in clinical trials. We are interested in the impact of culturally tailored versus standard counseling on decision making about testing, satisfaction with testing decisions, psychological functioning, and surveillance. We are hypothesizing that the culturally tailored program will lead to higher rates of test result acceptance and greater satisfaction, and that women who receive the culturally tailored protocol will report larger decreases in cancer-specific distress and greater utilization of cancer screening compared to women in the standard genetic counseling program.

We are conducting a randomized controlled trial of women age 18 or older who were recruited from clinical facilities and community oncology programs in Philadelphia, self-identified as being African American or black, and who had a 5 to 10 percent prior probability of having a BRCA-1 or BRCA-2 mutation based on their personal and family history of the disease. We used a standard genetic counseling format that was developed at Georgetown University that provides education about hereditary breast cancer susceptibility genes and the process of genetic testing; a personalized assessment of the likelihood that they have a BRCA-1 or BRCA-2 muta-

tion; and information about the benefits, limitations, and risks of genetic testing.

Women who are randomized to the culturally tailored protocol receive the same standard education plus an individualized discussion of cultural beliefs and values that our prior research has shown to influence decisions about genetic testing in this population. For instance, women talk about how their religious and spiritual beliefs would influence their decisions about having a genetic test and how concerns about family members might influence their decisions about testing and their responses. We used this approach as more of an individualized discussion, rather than a standard message about how religion and spirituality might be relevant to decisions about genetic testing, because we wanted to keep the protocol consistent with the overarching principle of nondirectiveness in genetic counseling. For example, we felt that it was inappropriate to tell women they should have a genetic test because God facilitated the development of this service and made it available. We wanted women to really think about how their own individual beliefs and values would influence their decisions about genetic testing. Parenthetically, I should say that the counseling protocol was delivered by a white masters-level certified genetic counselor, reminding us of Ms. Bennett's description of the limited ethnic and racial diversity of the genetic counseling workforce.

We seriously considered hiring an African American genetic counselor to deliver the culturally tailored protocol, because there was concern that having this information presented and discussed with someone not of the same ethnic or racial background might not be credible or effective. On the other hand, we concluded that specifically recruiting an African American genetic counselor would have limited generalizability. So ultimately we used the most qualified person, and that person happened to be white.

Following education and genetic counseling, women had an individual appointment with a medical oncologist. At that point, if women were interested in having genetic testing, a blood sample was drawn. Women were notified when their results became available and invited to come back in for a test result disclosure session that was conducted with the medical oncologist and our genetic counselor. There was then a 2-week postdisclosure test result follow-up telephone call and further follow-up telephone interviews at 1, 6, and 12 months. We are very proud that we have enrolled more than 200 women to our protocol, which means that they completed a baseline telephone interview and expressed some interest in coming in for genetic counseling.

We attracted a fairly highly educated sample. Close to 70 percent have some college education or have graduated from college. At the same time, a slight majority of women have an income less than $35,000, the median income level for Philadelphia residents. So, in contrast to other populations of women at high risk, we are not getting a high-income population.

We were interested in the process of recruiting and retaining women in our study. With respect to recruitment, we first wanted to discover the proportions of eligible women referred from clinical and community resources. We realized we couldn't rely on the traditional referral mechanisms within our cancer center for African American women participants in this study, so we developed a referral network that consisted of clinical and oncology community resources. We wanted to find the most effective place to identify women eligible for the study. Once we identified eligible women, we were also interested in determining how many women chose to participate in the program, and what factors were associated with decisions to participate.

We expected that eligible women would most likely be identified from oncology settings including mammography clinics and places where women were receiving oncology care for breast cancer or were being followed by a medical oncologist. We also expected that study enrollment rates would be greater among women who were recruited from these settings, compared to those recruited from general medical facilities and community oncology resources. We spent a lot of time thinking about the most effective ways to recruit women into this study. Our referral network consisted of seven clinical facilities that included the University of Pennsylvania's hospital and other facilities that had a high proportion of African American patients, such as community hospitals that were located in areas that were densely populated with African Americans. Women were referred to this study by physicians, clinic staff, and research personnel at each of those sites. Women were told about the program, they were given an informational brochure that described the purpose of the study, and those who were interested completed a referral form if they wanted to be contacted about participation.

Before we implemented recruitment, we conducted a small pilot study to find out from women what would increase the likelihood they would participate in the study. We were told that recruitment materials needed to emphasize that participants would get something out of it. Therefore, we emphasized that they would get breast cancer risk information in recruitment materials. Women reacted negatively to the suggestion that genetic testing was required as a result of participating in this program. So we emphasized in the recruitment materials that genetic testing was

optional. And it was, because our goal for the genetic counseling was to help women make an informed decision about whether or not testing was right for them.

Women encouraged us to appeal to their sense of altruism and emphasize that this study was important not just for their own health, but for the health of other African American women. So, the materials emphasized that African American women were needed to participate in this type of research to develop more effective counseling strategies.

From February 2003 to August 2004, a total of 783 women were referred to the program. We have now surpassed that number; I think we have had more than 1,200 referred. Most women (63 percent) were referred from general medical practices. Of the women who were referred, 21 percent (164) were eligible for study participation based on their personal and family history of disease, and most of these eligibles came from oncology settings (44 percent) and not general medical practices (11 percent). Of the eligible women we asked to enroll, 62 percent accepted, that is, they completed the initial telephone interview. We did not require women to come in for genetic counseling, because decision making about counseling and testing is one of our study outcomes. We are pleased that our enrollment rates are similar to the rates observed in other populations. We looked at predictors of decisions about study enrollment. We found that women who had a strong family history of cancer and those who were referred from oncology or community oncology practices were most likely to enroll in the study, and those from oncology clinics were more likely to participate in genetic counseling (Halbert et al., 2005).

Once recruited, we wanted to know if women continued to participate. We recently looked at retention in the study, evaluated at completion of the first follow-up assessment or the 1-month follow-up telephone interview, the first point at which the outcomes of genetic counseling are evaluated. I think it is important to emphasize that women were not provided with a financial incentive to complete follow-up telephone interviews and were only reminded that they would be contacted again by telephone for the follow-up surveys. So, we used a minimal contact procedure to remind women about the follow-up telephone interviews. We were very pleased to see that 73 percent of women were retained in the study, and only 27 percent were lost to follow-up. We found that women who were employed were significantly (73 percent) more likely to be retained in the study.

We next looked at decisions about genetic counseling and testing, starting with whether women were even interested in having a genetic test, by

exploring their intentions to test for BRCA-1 or BRCA-2 mutations. We next looked at participation in genetic counseling, that is, whether women completed the pretest education and counseling session. Finally, we looked at whether or not women received their genetic test results. We looked at the relationship between family history of cancer and BRCA-1 prior probability, at intent to test, and participation in counseling. We also wanted to know if there were differences in test result acceptance among women who received culturally tailored versus standard genetic counseling. We predicted that risk of mutation would strengthen and fatalism about cancer would weaken intentions to test, that probability of mutation and strong family history would strengthen participation in counseling, and that culturally tailored counseling, certainty about cancer risk, and some demographic factors such as marriage would increase test result acceptance.

With respect to genetic testing intentions, 30 percent of eligible women in the trial said they would definitely have a genetic test, and 32 percent said they were not considering having genetic testing. This suggested to us that pretest education and counseling may be very important to women, because they have not made a decision about whether or not they want to have genetic testing at this point. Genetic testing intentions in our sample are much more diverse compared to levels of interest in white women, 75 percent of whom intend to test.

A stronger family history and the perception of a likelihood of a BRCA-1 or BRCA-2 mutation turned out to be significant predictors of greater levels of interest in testing before pretest education. We found that 50 percent of all the women enrolled participated in pretest education and counseling, and those recruited from oncology clinics were most likely to participate in genetic counseling compared to women who were recruited from community and general medical practices (Halbert et al., 2005). Although 50 percent does not seem a very high proportion of women, it is actually much higher than the rates reported in other groups. A recent study reported 20 to 30 percent of women participating in genetic counseling. So we felt we were reaching a cohort of women who were interested and who will participate in genetic counseling.

However, test result acceptance tells a different story. In the total sample of women, and this was everyone who completed a baseline telephone interview, only 22 percent of women received their genetic test results. When we looked at the subset of women who had participated in genetic counseling, only 47 percent of those women received their genetic test results. Overall, it is not a very high uptake rate of genetic test results

in this population. We also looked at test result acceptance by the type of genetic counseling they received, and we found no differences in test result acceptance among those who received culturally tailored or standard genetic counseling. However, we found that women who were married and those who were less certain about their risk of developing breast cancer were most likely to receive their genetic test results. I think our finding that certainty about one's risk of developing cancer has implications for genetic counseling is important when we think about this particular population. Others have reported the high prevalence of variants of uncertain significance in the African American population, and that held true in our population. If women think that they will receive definitive information about their risk, the issue of variants may be an important part of counseling that needs to be addressed up front, so that women know what to expect.

We were interested in women's satisfaction with genetic counseling and the impact of culturally tailored versus standard genetic counseling on psychological functioning. We recognize there are multiple time points at which these outcomes could be evaluated. Using a self-administered questionnaire, we measured women's satisfaction (a measure of improved coping and lessened anxiety) immediately after the pretest education and counseling session when the experience was fresh in their minds, and we evaluated breast cancer-specific distress at the 1-month follow-up telephone interview.

Overall, 96 percent of women said that they were very satisfied with the counseling they received. However, only about a quarter of the women strongly agreed that the counseling helped them to cope better and lessened their general worries, and these women were more likely to have received culturally tailored, rather than standard, genetic counseling. This may be because during the culturally tailored protocol women talked about their beliefs and values, were asked to think about what types of resources they would use to cope with their genetic test results, and considered how they would use those resources to disseminate information to their family members. These discussions may have lessened worries among women in that group and also helped them to cope better with their risk (Charles et al., 2006).

We didn't see any differences in breast cancer-specific distress between those who received culturally tailored or standard genetic counseling. As others have reported, there was a decrease in both groups of women. Because participation in genetic counseling is an important outcome, we examined changes in breast cancer-specific distress based on whether women had even participated in counseling, irrespective of the type. There are no differences

at baseline, but at the 1-month follow-up, women who participated in genetic counseling had a greater change than those who declined participation, suggesting a value for genetic counseling in this respect.

In summary, we have spent a lot of time thinking about ways to recruit women into our genetic counseling program. Our experience shows that it is feasible to recruit African American women to participate in hereditary breast cancer research. We have expanded the diversity of the population in the clinical cancer risk evaluation program at the University of Pennsylvania. We also found that once women enrolled in this study, most are willing to participate in the clinical genetic counseling research protocol, and 50 percent will complete genetic counseling. Even though 50 percent complete genetic counseling, we did find that acceptance of BRCA-1 and BRCA-2 test results is somewhat limited and doesn't vary based on whether counseling is standard or culturally tailored. We also found that there were no differences in cancer-specific stress among women who receive culturally tailored versus standard genetic counseling. However, our data suggest that culturally tailored counseling, because it incorporates discussion of religion and spirituality and other cultural beliefs and values, may be more effective in addressing some aspects of worry and coping immediately following genetic counseling. Lessened worrying and more effective coping may explain our relatively low test result uptake rates. If women feel less worried and think they can cope with their risk of developing cancer, they may conclude that genetic test results won't help them to address those issues.

We think that genetic counseling might be beneficial to African American women regardless of the type provided. We have not yet evaluated the effect of genetic counseling on risk management behaviors, but intend to do that in the future. This has only been explored in one other group that focused on African American women from a single BRCA-1 kindred, so we are excited to be near the end of the study, where we will have 12-month outcome data on screening behaviors. We also need to know more about the long-term effects of genetic risk assessment, particularly with respect to the process of communicating genetic test results to family members from women that choose to receive results. We also need to look at uptake of test results among relatives of mutation carriers. Anecdotally, we have not seen substantial uptake in this group, so that is something we are really interested in exploring.

Dr. Ganz: I wondered about the marital status findings, and if they might reflect a sense of security for a woman; that she already has a partner, she

may have discussed it with her partner, she may not be worried about having to tell a new partner; or she has fewer financial concerns as married people generally have better incomes. I don't know if you looked at income as a barrier.

Dr. Hughes-Halbert: We did find a relationship between income and receipt of genetic test results. I forgot to mention that we had institutional support to cover the costs of genetic testing, so that was not a problem for women in this study. I agree that the marital effect may mean that the availability of a supportive partner, who might be encouraging women to have genetic testing or may be serving as a source of support, is important to testing decisions among African American women.

Dr. Ganz: For the single younger women that we test, it is quite a burden. There is the burden of "Yes, my mom has had breast cancer, and I am worried about that," but if she has the test and it is positive, that means quite a different level of concern. So I think in the African American community, where there may be a lower rate of marriage as you showed in your sample, it may be one of the barriers.

Dr. Hughes-Halbert: It could well be. Thank you for making this point.

Ms. Bennett: Did you correlate results with whether they had children or sisters?

Dr. Hughes-Halbert: We have data on sisters and children, but we have not looked at the presence or absence of children as a predictor of test result acceptance. That is something we can do, although at the moment I do not remember the proportion of women with children.

Dr. Weitzel: When you said acceptance of results, does that mean the percentage that started testing or the percentage that started testing and subsequently accepted the results that were in hand?

Dr. Hughes-Halbert: This was getting results, either positive or negative. At baseline, test result acceptance is based on everyone who enrolled in the study, so in the total sample 22 percent participated in genetic counseling and testing and received their test results. Of women who participated in counseling, 47 percent had testing and received their results. Of the small

number of women who participated in genetic counseling and provided a blood sample for genetic testing, the majority of women received their test results.

Dr. Weitzel: Did you have any ethical dilemmas, where you had a positive in hand and somebody didn't want to know about it?

Dr. Hughes-Halbert: Not that I can recall. We cannot make someone get their genetic test results, regardless of what they may be.

Dr. Ramsey: Do you think that trust in the health-care system was a factor in your results?

Dr. Hughes-Halbert: I actually do not for this population. When we asked women about their reasons for declining genetic testing, only about 1 percent said they distrusted the medical community.

Dr. Marc Schwartz, Associate Professor of Oncology and Co-Director, Cancer Control, Georgetown University: Are you saying that the 50 percent who had genetic counseling did not get their results? They provided DNA.

Dr. Hughes-Halbert: They did not necessarily provide DNA.

Mr. Thomas Kean, Executive Director, C-Change: You briefly spoke at the beginning about altruism as a motivation. I am assuming that includes altruism in the sense of benefit to a woman's family from knowing her results. Therefore, if altruism was one of the original motivations, have you speculated about why 50 percent did not want to know at the end of the day?

Dr. Hughes-Halbert: I do not have a good answer. It was surprising that so few women came in for genetic counseling and even fewer came in to receive their genetic test results. I do not have a good reason for it. In our focus group we asked if women talked to their family members about their cancer. They did not, not because they were selfish and didn't think their family members could help them, but they did not want to burden their family members. So, altruism might be a motivating factor for participation in the study, but women might be reluctant to share information that would worry or distress their family members.

Dr. Khleif: I just want to go back to the numbers. Out of 100, only 20 had genetic counseling?

Dr. Hughes-Halbert: Of the 157 who enrolled in the study, 22 percent participated in genetic counseling and received their genetic test results. For us, it was receiving the genetic test results that determined who was classified as an accepter. Of the 157, 50 percent participated in genetic counseling, so it is 50 percent of 157. Of those who participated in genetic counseling, 47 percent went on to get their genetic test results.

Dr. Khleif: Women who received genetic counseling did not necessarily get tested. But women who were counseled and tested usually received their test results?

Dr. Hughes-Halbert: Correct.

Dr. Khleif: What were the causes of difference in interest in testing between African American women and white women?

Dr. Hughes-Halbert: That is a really good question. Other work has shown that African American women do not report high levels of knowledge about genetic testing. They also have not heard or read a significant amount about genetic testing for inherited disease when compared to white women. This could explain why they are less interested in genetic testing at baseline compared to white women who are interested at baseline because they have greater exposure to information about testing. So, I think that lack of exposure to information about the availability of genetic testing and limited knowledge about breast cancer genetics are important to racial differences in interest in testing between African American and white women.

Dr. Khleif: Other than education, there are no cultural reasons?

Dr. Hughes-Halbert: I'm not aware of empirical studies that have evaluated cultural differences between African American and white women within the context of genetic counseling and testing for inherited breast cancer risk. We have looked at differences between blacks and whites in knowledge about breast cancer genetics and exposure to information about genetic testing for inherited breast cancer risk, and we have found significant differences between African Americans and whites in these factors. You might be ask-

ing why we choose to focus on cultural beliefs and values in blacks when those might be issues that are relevant for all people. Is that what you are getting to?

Dr. Khleif: I am interested in whether there were cultural beliefs other than education that would make a difference.

Dr. Hughes-Halbert: We have not evaluated racial differences in cultural beliefs between African American and white women, and I am not aware of any studies that have looked specifically at differences between blacks and whites and the role that cultural values and beliefs might play on interest in genetic testing. But there is research that has shown global differences between blacks and whites in terms of some beliefs and values, such as religion, spirituality, and the importance of family relationships.

Dr. Ganz: To be eligible to come in for genetic counseling, did the women have to have some level of risk so they would be appropriate for counseling? So, of these quite appropriate women, 50 percent were declining?

Dr. Hughes-Halbert: Right.

Dr. Weitzel: I presume a good portion of them had breast cancer because that is where our testing is most informative. You had a difference in source of referral, whether it was community based or oncologist's office. Does that reflect proximity to their breast cancer diagnosis? We do see time course interest in genetic testing as well as what they consider about management.

Dr. Hughes-Halbert: We did have a fairly high number of women who were newly diagnosed, and that could very well have been a factor.

Dr. Weitzel: There may be differences based on how long it has been. The oncologists making the referral are more proximal to the testing process.

Ms. Lochner Doyle: Reimbursement Issues: I am a current procedural terminology (CPT) advisor to the American Medical Association (AMA) CPT editorial panel, and I serve on the Health Care Professional Advisory Committee to the AMA. I also have been studying integration of genetic services into health plans for about the last 15 years. So I hope I have

something of value to share with you today. I plan to set the stage for you on understanding some of the strategies for billing for medical genetic services. I emphasize that there are huge data gaps in this area. I will discuss the reasons to study this issue in the first place, who does the billing, what the current picture looks like, followed by how we got here, and then I'll discuss some for strategies for improving reimbursement for cancer genetic services.

Why explore reimbursement? I am the head of genetic services for the Washington State Department of Health, and I have been looking at this for a long time. One reason involves the question of access to these services that I think is the focus of today's meeting. From a state perspective, as Dr. Greene noted, we have concerns about the workforce shortage. What is the wait time to be able to be seen? I get calls on a weekly basis from people out of state who are wondering if they can come up to one of our 15 regional genetic clinics to be seen, because the wait time in their state is so long. That puts a further drain on our already limited supply of providers. I think this is a very important issue.

We also recognize that there have been shrinking fiscal resources. As Dr. Weitzel was saying, there is a higher expectation among health administrators that the clinical services be self-sufficient. I don't think they will ever be self-sufficient, so we really do need to think about articulating the downstream funding that comes into institutions because of medical genetics services. But I think the greatest fear for me in my public health role is the potential hazards: missed opportunities to promote health or ill-advised medical decisions made because people do not have access to quality medical genetic services.

We have talked already about the various players who are billing for genetic services: medical doctors trained in genetics or other fields, Ph.D. laboratory directors; genetic counselors, and perhaps others. We held a series of focus groups with specialty providers in primary care (including OB/GYN), neurology, oncology, endocrinology, and psychiatry in both Eastern and Western Washington to try to identify what level of genetic testing and counseling we might anticipate being ordered by some of the other providers and whether the primary care or specialty care providers were meeting patient needs.

We learned that specialists were generally comfortable with specialty-related genetics and knowledgeable about available resources. It was interesting that oncologists were far more likely to perform genetic counseling and testing and the least likely to discuss ethical or social issues. Primary

care providers made it clear to us that they usually were not interested in providing these services, and they were far more likely to refer patients out for genetic services. They felt that this was a complex field; they had only 10 minutes to spend with a patient, and learning about genetic advances would be a waste of their time, given the rapid pace of change in the field.

I want to share with you what is happening now across the country, not just in Washington State. In my role as the principal investigator on two separate Health Resources and Services Administration grants that we have rolled into one, called the Genetic Services Policy Project, I have learned that increasingly many payors are including within their policies language specific to genetic services advocating for pre- and posttesting genetic counseling. The discovery of BRCA-1 and 2 and testing for mutations in these genes were the start of much of this policy development. We also have found that laboratory services in general are fairly readily reimbursed and at a much better rate in fact than clinical services, although reimbursement rates vary across the country.

The two groups that are least likely to be reimbursed are the Ph.D. geneticists and the genetic counselors. Physicians and nurse practitioners can bill, perhaps not at a favorable level, but at least there is a mechanism for recouping some costs. I looked at the 13 largest payors including Medicare and Medicaid in Washington. At present, of those payors, six accept genetic counselors billing independently using their national provider identification number. One, Kaiser Permanente, is in the process of changing billing software to allow genetic counselors to bill. One allows genetic counselors to bill, but only under a physician's name, and five do not cover genetic counseling at all. Washington State Medicaid reimburses for nonphysician masters-level counselors billing under their own name and has for some time.

What about the experience of laboratories, for example, one of the largest, Myriad Genetic Laboratories, Inc.? Their reimbursement rate is greater than 90 percent, and over 90 percent of patients receive some form of third-party coverage, including 12 percent of patients by public funds, Medicaid, Medicare or TRICARE. Three to four percent are covered by the Myriad assistance program, which is there to help patients work with their insurer, although there is an element of uncompensated care there as well. The remainder are self-pay (Personal communication, William Rusconi, Myriad Genetic Laboratories, Inc.). More state-by-state provider

information from our genetic services project can be found at our website at http://depts.washington.edu/genpol/.

We have a patchwork quilt across the country when it comes to reimbursement: some plans pay, some plans don't, some plans pay higher levels than others. How did we get there? Medical genetics is a fairly young field with a limited history available to payors because through the 1970s and 1980s, most services were covered by grants and provided to patients free. It was not until these grants and federal funds started shrinking in the late 1980s that suddenly the genetics community woke up to the need to develop billing mechanisms and join the reimbursement age.

That is when the American Board of Medical Subspecialties ruled that the American Board of Medical Genetics could not provide certification of genetic counselors and Ph.D.s anymore. Also, the vast majority of services focused on obstetrics and pediatrics with many public policies and national laws influencing payment of pediatric and obstetric services but not services focused on adults. For example, the National Sickle Cell Anemia, Cooley's Anemia, Tay Sachs, and Genetic Diseases Act (1976), the Omnibus Budget Reconciliation Act (1989), or the Maternal and Child Health Block Grant all influenced reimbursement of pediatric or obstetric services. Because of the very short track record of billing, there has not been a lot of data about genetics services, and thus a huge data gap exists.

When we consider CPT codes and how we can systematically collect data about service utilization, our best bet will be claims data. In my state we have 15 regional genetic clinics that provide me with service utilization data. That tells me what is going on in the genetics community; it doesn't help me with what the obstetricians or the oncologists, among others, are billing for, or services they are providing. Claims data, however, will not show me who is billing for genetic counseling. I can get the testing data, because there are specific CPT codes for the tests, but almost all physicians use the evaluation and management codes for office visits and consultations, and those codes do not allow me to differentiate between a genetic evaluation and a consult for chronic ear infections.

Again, we lack billing mechanisms because we are fairly new to this. Historically, the CMS, formerly known as the Health Care Financing Administration, issued universal provider identification numbers (UPINs) only to physicians. Allied health care providers had to be recognized by Congress in the Medicare statute as additional recognized providers, which included nurse practitioners, physician assistants, clinical psychologists, and

a few others. The fortunate thing about the HIPAA is that it required CMS to develop a national provider identification (NPI) system that includes medical geneticists and genetic counselors, among others. This should go into effect in October of this year.

There were very few CPT codes prior to 1994, the first year that the American College of Medical Genetics put in an application to expand CPT codes specific to genetic services. Regrettably, the ones put forward for clinical services were denied, but fortunately the ones put forward for laboratory services were adopted. Since then, CPT has come back and asked for an entire update and revamping, using a modifier system. All of their laboratory codes for CPT are specific to genetic services. So from the laboratory side, the mechanics for billing that were not in place are in place now and working well.

There has been a realization that we needed to have better documentation at the clinic level in order to support the codes we were using. If physicians or other providers have been seeing the most complex cases, they should ensure that they can document the amount of time spent with a family and the complexity of the case, so they would be in compliance with the code in case of an audit.

Several people this morning were talking about the need for an evidence base. That presents somewhat of a challenge in the world of genetics, particularly genetic counseling, because the desired outcome is not necessarily improved health but rather the empowerment of the patient to make the most appropriate medical decision. Is the outcome whether the patient chooses to pursue genetic testing or whether she has a prophylactic mastectomy or oophorectomy? We have to be very careful to define the outcome properly.

I would like to remind people that CPT is basically a common language describing what service was performed. It was first created by the AMA in 1966 for claims processing, administrative management, research, and medical education, revised annually, and adopted in 1983 as part (Level I) of Medicare's Healthcare Common Procedure Coding System (HCPCS). The other common language codes are the ICD-9s. The CPT says what was done, the ICD-9 says why it was done. From a claims data perspective, that is the best way to find out what is happening in billing and reimbursement. Unfortunately it does not always work because we do not always have the appropriate codes.

I mentioned the new section on genetic testing code modifiers, which allows us to discover what tests are being performed. I am hoping that, in the near future, the NPI number will also help us in terms of recognizing

the categories of individuals who are ordering these tests. We were able to have a new code effective January of this year, specifically for genetic counseling as provided by trained genetic counselors. The Blue Cross and Blue Shield organizations were our staunchest advocates in getting this new code, yet the Blue Cross Blue Shield plans are organized state by state. In my state, Blue Cross and Blue Shield are two separate payors; one accepts billing for genetic counseling and one does not. Yet for the purpose of trying to obtain the CPT code, they were the ones who were strongly in favor of approval. The code (96040) states, "These services are provided by trained genetic counselors and may include obtaining a structured family genetic history, pedigree construction, analysis for genetic risk assessment, and counseling of the patient and family. These activities may be provided over one or more sessions and may include review of medical data and family information and face-to-face interviews and counseling services." My hope is that this code will allow us to see specifically who is providing genetic counseling.

So, is this new code being used? The answer is yes, but it is not always being reimbursed. I have been compiling data from my colleagues across the country on rejected billings: why they are being rejected, and what are some of the limitations? Some of them are simply software edits. I mentioned the example of Kaiser Permanente earlier. The AMA does not release the language of new codes very far in advance because they do not want software developers getting it wrong. A new code requires payors to edit software and create new programming. Furthermore, AMA made a recommendation to CMS that this code for genetic counseling be a bundled service. The CMS recognized that genetic counseling can be performed by physicians as well as trained genetic counselors, and that from their perspective, genetic counseling is an integral part of a primary service and therefore is not eligible for separate payment.

That is the bad news. The good news, however, is that there is a resource-based relative value system (RBRVS) utilization committee that determines whether or not a new code should be given a value. The genetic counseling code was given a relative value unit (RVU) of 0.98. This rate is then multiplied by the published CMS fee schedule to arrive at a value for the service. So even if CMS has chosen not to pay counselors for the service, that does not mean other payors cannot. It also opened the door for physicians to bill for the genetic counselor's time. I am going to come back to that because I know that is a very confusing point. We have learned from several payors that they are adopting the CMS language, and therefore they are not recognizing the new code. In other circumstances, payors only

provide for services when rendered by a licensed health-care provider, and at present there are only five states that license genetic counselors. This is a payor policy.

Just to go back for a moment, the Ph.D. clinical geneticist certainly would be eligible to use the 96040 code. However, CLIA regulations require that only M.D.s may charge a professional fee for interpretation of results, which means there is no mechanism for a Ph.D. laboratory director to bill for services. The American College of Medical Genetics is trying to revise that. But, this is a very small subset of the overall genetics provider population.

Beyond the mechanics of CPT codes and ICD-9 codes, whether or not someone is licensed, and payor policies, we also have to recognize the different types of payors—indemnity plans, traditional fee for service, health savings accounts, and so on—may provide different ways to pay for genetics services. Health savings accounts are a small but growing market. About 30 percent of the largest employers right now are insisting that a health savings account be offered to their employees. The accounts provide a certain level of funding, and the employees then choose how their health-care dollars are spent. There are very high deductibles before the insurance begins paying. This kind of plan is attractive to young, very healthy employees who can carry their account dollars over each year and build up the account like a 401K. Others question whether consumers can make good decisions about health care and worry that they will try to save money at the expense of preventive or other worthwhile or needed care.

There are clinics that have contracted services with specific payors. Group Health Cooperative doesn't have that many providers in eastern Washington State; so they have specific contracts with clinics to provide services for their enrolled clients. Capitated service contracts are basic managed care contracts. Then there are the public payors, Medicaid, Medicare, and TRICARE. Why does it matter? Because these payors have different rates and different rules, they raise different issues that make it complicated to strategize on ways to have the services reimbursed.

I want to spend a few minutes talking about the influence of Medicare, because it is such an important payor. Many plans simply adopt the published guidance or policy of Medicare. Because antitrust laws do not apply, Medicare is one of the few payors that can publish its rules and fee schedules, and thus it ends up setting the stage for all other payors. Many Medicare policies are established by Congress, so they aren't necessarily best medical practices or even common sense in some cases, but they are

the rules and regulations that CMS must abide by. The Medicare policy in statute requires that tests performed for screening purposes in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute. Potentially, a lot of cancer screening is going to be eliminated by this requirement.

Dr. Straube raised the issue of local versus national coverage decisions. There are 28 contractors that make coverage decisions for CMS at the local level. If enough of those local level decisions become routine or standard, they can become national coverage decisions, but they may not start that way. They all have to meet the regulatory standards. They have to be in a benefit category, such as diagnostic, not screening, related to the patient's management, reasonable and necessary. A family history is not sufficient for coverage.

I mentioned "incident to" services earlier. If a provider is listed in Medicare law, such as an advanced registered nurse practitioner, and that person meets certain criteria (for example, provides services integral to physicians' services, that are commonly part of a physician's bill, that are usually provided in an physician's office by an employee of, and directly supervised by, a physician), then the work they do can be billed as incident to that of the physician provider. There are complications to this, however. Many physicians have become employees of physician billing groups, particularly in academic institutions, and their staff became employees of the hospital. The requirement that the staff be under the physician's direct personal supervision means that the physician needs to be in the same office suite, not just in the same facility but on the same floor, and the employee is a W2 employee of the physician, or the physician and employee are W2 employees of the same entity. This is often not the case for genetic services, where the physician might be physically separated on a different floor of the building. Billing for genetic services would not be possible under that sort of arrangement.

So there are many different payor rules. Medicare can vary from state to state, depending on local coverage decisions. Lots of plans have preferred providers. Even Medicaid has providers that must enroll to identify that they will accept Medicaid payment amounts and not ask for additional payment from the patient. And there are differing payor policies for covering out-of-state laboratory services, which is obviously critical when dealing with cancer testing. Myriad makes an effort to be a recognized Medicaid provider in most states, but not when reimbursement levels are inadequate. So, Myriad is not a provider in the state of Washington, because the reimbursement level is less than 50 percent, and that means that in Washington

State, many of the clinics bill through their parent institution at a loss as was described earlier, in order to get the patients tested.

Some other payor policies that affect reimbursement involve licensure. There are definitely plans that only reimburse for services provided by a licensed provider, but we have worked with several in our state to help them change the language in their policies to "appropriately credentialed provider," which could be somebody who is certified by the American Board of Genetic Counseling. We worked very hard in our state to develop a template for credentialing in plans the masters level or Ph.D. prepared genetics provider, which mirrors what the M.D.'s have to provide in terms of their credentials. Obviously, they are not licensed, but they do have to have medical malpractice insurance, they have to have a certain level of training, and they have to have national credentials, among other things. So we came up with a template that allows the various plans to recognize the non-M.D.'s as preferred providers as well.

The use of multiple providers also poses problems. A multidisciplinary team consists of many different people seeing the person. Some payor policies provide for acceptance of only the first bill submitted using the CPT/ICD-9 code. So other bills need to have different CPT and ICD-9 codes, or providers need to submit bills quickly to get paid before others are in line. This is also a problem for telemedicine, where there are multiple providers, one on each end of the communication. Some states have been able to work out that both will be paid. I am pleased to say in Washington State that is true for pediatric referrals at least. So this is an issue with multiple providers when you have a multidisciplinary team.

We frequently hear from consumers that their payors denied reimbursement based on a decision that the testing was experimental or not medically necessary. But, the top reason for complaints to our Office of the Insurance Commissioner is denial of what the patient thought was a covered benefit. However, on review of the plan, either the employer has very specifically excluded coverage of genetic services or the plan itself has made the exclusion. Sometimes plans or employers will limit benefits to assisted reproductive technologies, for example; other times limitations are pretty global. These are simply payor policies, as mentioned before.

I promised I would suggest some possible strategies. Obviously, we can all use our influence to advocate for standardized laboratory and clinical reimbursement policies. I think the purpose of HIPAA was to reduce inefficiencies through greater standardization; but I do not think we are quite there yet. There is some lobbying now for genetic counselors to be

included in the Medicare law and regulation as allied health-care providers. That would certainly open up billing in their own name for services "incident to," if they fit the criteria.

Payors could be educated regarding the benefits of coverage under existing CPT codes. That can include either changing existing licensure language to appropriate credentialed language, as I noted earlier, or simply including genetic counselors or Ph.D. geneticists as preferred providers. Last but not least, we can advocate for state licensure of genetic counselors, as the National Society of Genetic Counselors has been doing vigorously for the last several years.

The situation is quite complicated with many payors, many providers, and many policies, so change will take time. I think that we are very much left with an approach in which, one plan at a time, we try to make the policies as good as we can for integrating genetic services into mainstream health care.

Dr. Bach: I wonder if you have had any experience with a situation where a practitioner orders a genetic test, let's say it is BRCA-1 or -2. The specimen to be sent to the laboratory that will perform the test often exists at a hospital where the patient had a surgical procedure. The patient was discharged before the practitioner ordered the test. Now who pays for the transmission of the test specimen to the lab facility? Has that been an issue? We were concerned about that when we first talked about this with California.

Ms. Lochner Doyle: I have not heard that to be an issue for cancer, but it has been an issue in the past for neonates transferred, particularly from Alaska to Washington State, when you cross borders.

Dr. Herbst: You mentioned that Myriad has some sort of assistance program. Are there any assistance programs to help patients with copayments for tests?

Ms. Lochner Doyle: Not really. It depends on the plan. If they have 80 to 90 percent coverage and if they have met their deductible, they might not have much copayment. So, people often come in at the end of the year, when the deductible has been met.

Dr. Herbst: They have a $3,000 test and they might have 80 percent reimbursement, but if that patient has a $1,000 or $500 deductible, that comes off the top, and then they pay the 20 percent. So if the reimbursement is

80 percent, the 20 percent amounts to $600 for the patient for the $3,000 test. And keep in mind, the cost-effectiveness comes from testing the family members once the mutation is known, and the cost for that single site test is around $500.

Ms. Lochner Doyle: Occasionally there is assistance or a patient's payment is written off entirely for some Medicaid beneficiaries.

Dr. Herbst: The trick in an assistance program is getting the patient to fill out the financial indigency paperwork for the assistance and to gather the tax documents to support the application; the limit on income is also quite low.

Ms. Lochner Doyle: And even once they do, it is often in excess of 6 to 7 months before they get word whether or not they will even be considered. If you go to the program Website, you will see that the reimbursement assistance program is geared toward helping patients work with their insurance company.

Dr. Weitzel: Which is unnecessary because of the third-party relationship with the billing. One of the reasons we do it that way is that, once we hand it off to them, they do the negotiation with the patient instead of our having to do it.

Ms. Lochner Doyle: This may sound hard-hearted, but I don't have that much sympathy for the financial situation of the labs. Although they have their research and development costs, once they have the test available, they are getting pretty well reimbursed compared to the clinical services.

Dr. Schwartz: Psychological Impact on Patients and Families: I am going to talk about the psychosocial and behavioral impacts of genetic testing for cancer susceptibility. By behavioral impact, I mean the impact of cancer susceptibility testing on rates of cancer screening and of preventive surgery.

What are the psychological consequences of cancer genetic testing? I am going to focus on BRCA-1 and -2 and HNPCC testing, since those are by far the most common forms of cancer genetic testing. The biggest concern as testing was developed and implemented was the potential for adverse psychological outcomes, most obviously the potential for carriers to

experience increased levels of clinical distress and diminished quality of life following receipt of a positive test result. There were also concerns about a false sense of security from those who received uninformative test results, those, currently affected with breast or ovarian cancer without a known mutation in the family, who received a negative test result and took it as some sort of a guarantee. Then there was also some discussion about guilt among true negatives, those with a known family mutation who test negative. There is clearly the potential for a beneficial psychological outcome, such as relief and reduction in chronic distress among true negatives, and even the reduction in uncertainty among positives, to the extent that they may have been assuming for years that they were certain to develop breast or ovarian cancer due to their family history—just learning that they do carry that mutation could reduce the uncertainty and have some beneficial psychological effects.

There was also some discussion about family communication; will probands communicate test results to their at-risk family members, would there be a potential for family conflicts about testing if an individual in the family wants genetic testing but perhaps the most logical person to start with testing is not interested? On the other hand, there is the potential for communication and discussion of health information among family members. Then, in terms of the behavioral impact of genetic testing, there is a whole list of management options, some of which are likely effective, such as breast cancer surveillance, chemoprevention, or prophylactic surgery; others less so, for instance, ovarian cancer screening. However, it is clear that without appropriate behavior change, genetic testing will not lead to reduced morbidity and mortality. Do carriers adopt prevention and risk-reduction strategies, and do noncarriers reduce their prevention and risk-reduction strategies to levels recommended for the general population? These are all important questions prior to the onset of testing. I will now review some of our own data and data from the literature on each of these outcomes and provide a sense of what the results of these initial studies from the first 10 years of testing are showing us.

We looked at the short-term impact of genetic testing on psychological distress among unaffected women from families with known BRCA mutations (Tercyak et al., 2001). From baseline to predisclosure of test results, anxiety stayed stable. On hearing results, there was an immediate and significant decrease in anxiety among women who received a true negative test result as one would expect, and a slight increase that was not significant among women who received a positive result. So at the immediate post-

disclosure session, there was a significant difference between the two groups, but it was really a function of the decreased distress among negatives; not a function of increased distress among positives.

We see exactly the same sort of thing in a Dutch study that followed women out to five years—postdisclosure reduction of distress among those who received a true negative result and essentially stable distress in those who received a positive result with the difference diminishing slightly at 5 years. But essentially, women who got a positive test result were no more distressed at any point that was measured in those 5 years than they were at baseline. Women who got a negative result seemed to have a small benefit (Van Oostrom et al., 2003).

In another of our studies of unaffected women and probands, the unaffected women from families with a known BRCA mutation showed a significant drop in cancer-specific distress at 6 months after a negative test and no change at 6 months after a positive test. Probands, that is, women from this cohort that had had breast cancer showed a small nonsignificant decrease in cancer-specific distress at 6 months whether their tests were positive or negative (Schwartz et al., 2002). Of the four groups, three—positive affected, negative affected, and positive unaffected—end up at the same place. The only group that is different is the negative unaffected group that were reassured presumably because they had neither the mutation nor cancer. So we are seeing reassurance benefit among those negatives; we are not seeing distress among positives.

If we evaluate distress at baseline, 7–10 days, 4 months, and 1 year after HNPCC testing, we see the exact same thing, a slight increase among positives in the very short term, leveling off out to a year, and that is contrasted with reduced distress among the negatives. The difference between the two groups is maintained at all posttesting intervals. Summarizing from these and other studies, we certainly see short-term increases in anxiety among carriers, but even in the very short-term postdisclosure period, distress levels are far below what we would consider clinical levels of distress. We see little evidence for long-term increases in distress among carriers. We see decreased distress among unaffected negatives over time (Meiser et al., 2004). Fewer studies have focused on distress following testing in affected patients, but those who have looked at it, including our group, have generally found no increase in distress and little decrease in distress among those who receive uninformative results. It does not appear that there is any false reassurance here. Women who receive uninformative test results are basically as distressed as they were prior to testing. There is some low-level chronic

distress, and it stays about the same for individuals who receive positive test results and individuals who receive uninformative test results, but drops significantly for those who get negative test results.

We recently evaluated long-term rates of family communication to various relatives a mean of 5 years and a minimum of 4 years following genetic testing. Rates of communication are uniformly high, over 90 percent communication to the mothers, sisters, and spouses of probands, high rates of communication to adult children, slightly lower communication rates to fathers and brothers, and as you would expect, substantially lower communication to children under the age of 18, but still about a 50 percent rate of communication to younger children. If we stratify those data by test result, the only differences we see are among the male first-degree relatives. Communication to brothers and fathers is significantly more likely if a sister or daughter has an uninformative test result, and there is no difference in any of the other groups. When we compare this to earlier studies, we also see very high rates of communication in the short term. Rates of communication actually don't increase very much over time. Communication typically takes place quickly after receipt of a positive test result.

There has been less research looking at the specific impact of genetic testing on family functioning, although it has been an ongoing concern. There are some data suggesting that women who did not share their concerns with their partners prior to testing reported more distress following testing, and that is regardless of test result. Mothers are more likely to communicate with older children, and, not surprisingly, those who reported a more open communication pattern at baseline are more likely to communicate with their younger children following the receipt of a test result. Interestingly, mothers who were more distressed prior to testing are more likely subsequently to communicate their test results to their children. We do not know exactly what to make of that, because we are not seeing distress differences increasing, we are just seeing it as a predictor regardless of the result. Another point is that although communication with first-degree relatives is quite high, there is some evidence, although just from one study that I am aware of, that communication with second-degree relatives is substantially lower.

Next, concerning behavioral impact, I will try to summarize studies on mammography use the year before and the year after genetic testing and for carriers and noncarriers. The most recent study from Belgium reported not much difference in mammography rates between noncarriers

and carriers before testing, but an increase from 59 to 93 percent in carriers in the year after testing (Claes et al., 2005). A study from 2000 found a significant difference at follow-up between carriers and noncarriers; carriers were more likely to be tested, but no change from pretesting to posttesting in the rates of mammography (Lerman et al., 2000). Another study found similar results, a higher rate of mammography among carriers, but again no change, or maybe even a slight decrease from the year before to the year after testing. If the results from this study are grouped by age; however, older women for whom annual mammography is recommended regardless of test result have mammography rates that are high and independent of test result. But for younger women, from 25–39 or 40–49, mammography rates are affected by test result and most significantly in the youngest group for whom mammography is not usually recommended. In that group, noncarriers have mammography rates of around 20 percent versus the carrier rate of 39 percent (Peshkin et al., 2002).

In summary, in these and other studies, mammography adherence rates are fairly high. We think that more recent studies are those showing higher rates of mammography among carriers. Across all studies they ranged from 59 to 93 percent in the year following the receipt of a positive test result. Rates were lower among noncarriers. I do not think that reflects a reduction in adherence among noncarriers. I think what it reflects is an appropriate drop in mammography rates among younger noncarriers. There is a significant effect of test results on the likelihood of mammography following testing. Age is the best predictor of which mutation carriers choose to have a mammogram in the year following testing versus those who do not, older mutation carriers being more likely to get a mammogram in the year following testing. We do not have data abut rates of MRI or breast ultrasound. Those are newer modalities that have not been evaluated in these studies.

Moving forward now to ovarian cancer screening, it is important to keep in mind that, although ovarian cancer screening is sometimes, but decreasingly, recommended for carriers who are not considering oophorectomy, there are no good data to suggest that it is effective. Nonetheless, we looked at rates of ovarian cancer screening following testing. First, we found significant increases in CA125 screening among positives (21 to 68 percent); no change among uninformatives, which makes sense because their risk is not being substantially modified from pretesting; and we found a significant decrease among those with negative tests, which you would expect, because there is no reason for CA125 screening of negatives (Schwartz et al., 2003).

A 0 percent rate of CA125 at baseline, going up to about 30 percent among positives and a little bit of an increase among negatives was found in another study (Botkin et al., 2003), and yet another study reported basically similar results (Lerman et al., 2000). Other ovarian cancer screening modalities such as transvaginal ultrasound also give essentially the same results—increases among positives, no change or decreases among uninformatives and negatives. Aggregating data from a number of studies, there is a 15 to 73 percent rate of transvaginal ultrasound in carriers, a very low rate in noncarriers. Same thing exists for CA125:, although the absolute rates may be slightly lower. Receipt of a positive test result is clearly associated with an increased use of both of those screening modalities. I think that noncarriers are exhibiting appropriate reductions in ovarian cancer screening. Predictors of ovarian cancer screening were psychosocial, perceived risk for ovarian cancer, and anxiety.

A study of colonoscopy after genetic counseling and testing in 98 men and women without a personal history of colorectal cancer from 11 extended HNPCC families found that at baseline there was no difference between men and women. One year after counseling and testing, there was an approximate doubling of colonoscopy use to 73 percent among carriers (16/22) and a slight decrease among noncarriers. Discovery of the carrier state led to increased use of colonoscopy, and there was a reasonable response of less use in the following year after a negative genetic test (Halbert et al., 2004)

Similar results were found in another study. Colonoscopy and flexible sigmoidoscopy screening was analyzed before and 6 and 12 months after genetic counseling and testing. Among negative testers, screening declined significantly after testing, and among those who tested positive there was an increase, though not statistically significant (Hadley et al., 2004). To summarize, after testing, 53 to 88 percent of carriers were being screened, and 8 to 16 percent of noncarriers were being screened. HNPCC carriers exhibit increased use of screening, and noncarriers exhibit appropriate reductions in screening. It is hoped when their 10-year screening interval comes up, noncarriers will return to screening, but we just do not have the data on that yet. Older age and the perception that screening gave some control over cancer were predictors for screening among carriers.

I will turn now to surgical management starting with bilateral prophylactic oophorectomy because that is a little more straightforward than mastectomy. Our group looked at rates of oophorectomy in the 12 months following genetic testing (Schwartz et al., 2003). Among posi-

tives just over 20 percent of BRCA-1 and -2 positives opted for bilateral prophylactic oophorectomy by 1 year. Rates were higher in BRCA-1 carriers than they were in BRCA-2 carriers as expected. Among uninformatives, that is, women who had breast cancer but received an uninformative (negative) test result, rates of oophorectomy were quite low, and among true negatives they were even lower. Incidentally, over 10 percent of our sample had already had prophylactic oophorectomy before testing.

Data on oophorectomy, a mean of 5 and a minimum of 4 years after testing, show a much higher rate of bilateral prophylactic oophorectomy—over 50 percent in women with previous breast cancer, just under 50 percent of those unaffected with cancer, and a substantial rate prior to testing. In this study, the predictors for surgery following testing were receiving a positive test result, age, and having a prophylactic mastectomy. So, women who had a prophylactic mastectomy were more likely to also have a prophylactic oophorectomy in the 5 or so years following testing (Graves et al., 2006).

To summarize, in North American studies, the rates for bilateral prophylactic oophorectomy range from 13 to 67 percent among carriers with intact ovaries prior to testing. Rates in European studies are somewhat higher, 31 to 75 percent. It is clear that the rates increase with longer follow-up. In our long-term follow-up study, more than half of the women who ultimately got a prophylactic oophorectomy did so after the first year post testing. Many previous studies have only gone out to 12 months, and so they are severely underestimating rates of prophylactic oophorectomy, because women continue to consider surgery, for example, when they complete childbearing. So with a younger cohort we are going to see longer lags between positive test results and oophorectomy. Predictors include older age, ovarian cancer risk perception, a family history of ovarian cancer, and those who were affected with breast cancer, in particular those who were affected with early breast cancer, which certainly makes sense. Having had a prophylactic mastectomy is also a predictor.

Turning to prophylactic mastectomy, which is more complicated, there are a number of overarching factors that affect rates of mastectomy. Rates in Europe are much higher than in North American or Australian studies. Cancer status is clearly related to rates of prophylactic mastectomy. Women who are unaffected carriers tend to have lower rates than women who have been affected with breast cancer but have completed all of their treatment, and those women have lower rates than women who receive genetic testing and a positive test result at the time of a new breast cancer diagnosis. Most studies have focused on 1 year posttesting, or some include a wider range

of follow-up times, but include a substantial portion of women who were tested within a year. So, long-term follow-up is a question.

An early study from our group looked at prophylactic mastectomy among unaffected women. Rates were extraordinarily low; less than 5 percent of unaffected mutation carriers opted for prophylactic mastectomy within that first year following testing (Peshkin et al., 2002). Our most recent study followed women to a mean of 3.5 years and showed a much higher rate of prophylactic mastectomy, approaching 30 percent among carriers. None of the true negatives opted for prophylactic mastectomy during that time (Graves et al., 2006). I think this higher rate clearly reflects the longer follow-up, but it also probably reflects a temporal trend that rates of prophylactic mastectomy are higher now than they were when our first study was done.

Review of other studies from North America and Australia shows a range of prophylactic mastectomy in unaffected women with a recent Australian and Canadian study reporting relatively high rates and older U.S. studies reporting rates of 15 percent down to substantially less, including one (Botkin et al., 2003) with no instances of prophylactic mastectomy after a 2-year follow-up. Rates in European studies are generally much higher, reaching over 50 percent in some studies.

In breast cancer survivors, that is, women who have completed primary breast cancer treatment, we carried out a study of rates of prophylactic contralateral mastectomy within 12 months of genetic counseling and testing. Prior to testing, 16 percent of survivors had a prophylactic mastectomy, a high percentage probably reflecting decisions made at the time of original treatment. Within a year of receiving positive test results, 18 percent opted for surgery. The rate for those who received uninformative test results (there are no longer true negatives because all women had breast cancer) was 3 percent (Graves et al., 2006).

In our 5-year study, we see even higher rates—almost 30 percent of carriers, again a low rate among uninformatives, and over 20 percent among newly diagnosed patients before testing. When we offered genetic testing to women at the time of their breast cancer diagnosis and returned the results in enough time for them to use the information to make primary surgical decisions, we observed almost a 50 percent rate of bilateral mastectomy among mutation carriers, and a surprising 24 percent rate among those with uninformative results. That result on further exploration was explained by instances of multiple preceding breast biopsies or failure to detect the indicator cancer on mammography, among others (Schwartz et

al., 2004). I should mention that our 50 percent rate among positives is substantially lower than that reported in a couple of other studies in this sort of population, including one by Dr. Weitzel where all of the positive women went on to contralateral prophylactic mastectomy. Other studies of newly diagnosed patients, including European studies, report a range of rates, some lower and some higher than ours, but all higher than we see in unaffected women.

Who chooses to have prophylactic mastectomy among unaffected women? Younger age, having children, and getting a positive test result are clear predictors. Among affected women, we see different things in different studies, but certainly a positive test result. We think the timing of test result relative to diagnosis is an important predictor. Among newly diagnosed women, when a physician is said to even discuss the issue of prophylactic mastectomy, they are more likely to choose that option. Affected women who are more distressed prior to genetic testing and those with a more extensive family history are more likely to have a prophylactic mastectomy subsequent to genetic testing.

There have been several studies over the last few years that have looked at the psychological effects and effects on the quality of life of having prophylactic surgery. Two very large retrospective studies from the Mayo Clinic cohort, going back 30 plus years, looked at prophylactic mastectomy among unaffected women with a family history of breast cancer and reported that at a mean follow-up of 14.5 years over 70 percent were satisfied with their decision. Three-quarters reported that their prophylactic mastectomy reduced their worry about cancer. About a quarter of the women, reported at least one adverse effect of prophylactic mastectomy, typically on sexuality or body image (Frost et al., 2000).

The second study from the same group looked at quality of life and satisfaction in women with a personal and family history of prior breast cancer a mean of 10.3 years after contralateral prophylactic mastectomy. Over 80 percent were satisfied with their decision; the majority would choose this surgery again. But again, 25 to 30 percent or so reported at least one adverse effect of prophylactic mastectomy (Frost et al., 2005).

We looked at quality of life prior to and then following prophylactic mastectomy among newly diagnosed breast cancer patients who had their genetic testing in the context of a new diagnosis. Baseline was pregenetic counseling, the point of enrollment into the study. We followed quality-of-life outcomes to 12 months, and observed absolutely no difference between women who chose to have prophylactic mastectomy and those who did

not. We stratified this in many different ways, including by test result and prophylactic surgery decision, and we still see no differences at all.

We see the exact same thing if we look at distress over time among both women who have prophylactic mastectomy and those who do not, either newly diagnosed or survivors. So, prophylactic mastectomy does not seem to be associated with adverse distress or quality-of-life outcomes, although one of the key motivators that women typically report when they consider this intervention is their opinion that prophylactic surgery may reduce ongoing worry and distress about cancer. There does not seem to be either a significant distress and quality-of-life benefit or harm.

To summarize, regarding the psychological, familial, and behavioral impact of cancer genetic testing, there is little evidence for significant adverse psychological outcomes or false reassurance following an uninformative test result. There are extremely high rates of communication between probands and first-degree relatives, with lower rates of communication to second-degree relatives. Communication with minor children is a more complex issue, and we have some ongoing studies looking at that and developing educational approaches to help families make those sorts of decisions about whether and when to communicate with younger children.

In terms of surveillance, mammography use increases following a positive test result. Mammography rates are high among carriers over age 40 and much lower among younger carriers. Ovarian cancer screening for better or worse also increases following a positive test result, but the rates remained relatively low, less than 50 percent in most studies. Colonoscopy rates increase among carriers and appropriately decrease for noncarriers.

Prophylactic oophorectomy rates are higher than mastectomy rates. Rates are higher for affected women and higher for newly diagnosed women. Rates appear to be increasing, both for mastectomy and oophorectomy, and psychological and demographic factors are important predictors of prophylactic surgery.

There are some future clinical and research issues that need to be addressed. In all of these studies, participants received extensive and highly competent genetic counseling. This has been in the context of the research setting, but we need to know the impact of testing in the absence of such counseling—for example, in primary care or via direct-to-consumer marketing. Whether we can extrapolate the lack of adverse psychological outcomes to testing delivered in the community is an open question. The traditional genetic counseling model may or may not be tenable in the future as demand increases and genetic testing for cancer becomes more

widespread. There are large parts of the country where genetic counselors are not available, and so it begs the question: what would the impact be if genetic counseling was delivered through alternate delivery models, such as telephone or Internet counseling? We are conducting a randomized equivalence trial, comparing telephone counseling to in-person traditional counseling.

We have heard a little bit about the availability of direct-to-consumer commercial counseling. One important factor that was touched on, but I think is important to consider about DNA Direct, is that their business model depends on people choosing to get tested. I question the objectivity of their genetic counseling, since one of the goals of genetic counseling is to help people make their own decision about whether to get tested. But DNA Direct doesn't get paid unless someone chooses to get tested. So, there are questions about what the outcomes are going to be among people counseled in that setting. There has been some preliminary work on Internet-based counseling, typically as an adjunct to genetic counseling, and I think more needs to be done.

We have heard about disparities in genetic testing among ethnic minorities and among lower socioeconomic status individuals. That is obviously something that needs to be considered when interpreting the results of all of these studies. These studies were done on affluent white women, primarily. How or whether outcomes will differ in other groups remains to be seen.

We are starting to see long-term follow-up studies. Most of these studies and much of the discussion and work on genetic counseling and testing have focused on the initial decision about whether or not to get tested. I think more work needs to be done looking at ongoing decision support. These are not decisions in many cases that need to be made immediately. They are decisions that are sometimes made years—particularly for oophorectomy, for instance—after the receipt of a test result. Patients may or may not still be in contact with a genetic counselor. So looking at decision support on an ongoing basis is important.

Finally, as genetic testing becomes increasingly integrated into clinical care, as in newly diagnosed breast cancer patients or with microsatellite instability testing in colon cancer patients, are the outcomes going to differ from the largely self-selected earlier adopters who were the participants in many of the studies I just reviewed? There is some evidence, for instance, that women who get a prophylactic mastectomy following a physician recommendation do worse over the long term than women who came to

that decision themselves. Whether that will be the same for genetic testing remains to be seen.

Dr. Weitzel: In your discussion of HNPCC, you mentioned the decliners had a follow-up in colonoscopy as well. Did you want to comment on that? I thought that was a concerning observation.

Dr. Schwartz: The decrease among decliners I am pretty sure was not statistically significant. It was pretty small, but clearly that decliner group is a group that is not well characterized in terms of their psychological outcomes and in terms of their screening and surgical outcomes.

Ms. Javitt: Surgery rates were higher in Europe than in North America. I am wondering if you have any reasons for that?

Dr. Schwartz: One of my main collaborators is in Amsterdam. Many of these studies were done in the Netherlands. According to her, and this is completely anecdotal, of course, physicians tell mutation carriers to have prophylactic mastectomy. It is not an issue of informed decision making, it is not an issue of personal choice. They say, if you have a prophylactic mastectomy your risk for breast cancer is reduced by over 90 percent, so have a prophylactic mastectomy.

Ms. Javitt: Is there a financial issue? Like in the national health-care system?

Dr. Schwartz: I think there is almost certainly a financial issue, although the vast majority of participants in U.S. studies are affluent and well insured. I think as testing moves out to a broader range of socioeconomic statuses and insurance levels, cost will become more of an issue. The majority of participants in these early studies, with certain studies being exceptions, had the resources to obtain a prophylactic mastectomy if that was the option they chose.

Henry Greely, Esq., Professor of Law and Genetics, Stanford Center for Biomedical Ethics, Stanford University: Implications for Access to Health and Life Insurance: In 1992 I wrote my very first piece about genetics and legal issues and discrimination, in which I predicted that

genetic discrimination was going to be a major problem, particularly with respect to employment, and that it would put our health-care financing system under substantial strain. I was wrong, for a variety of reasons which I will spend a little time talking about. The issues of genetic discrimination are nontrivial and significant; they are, however, getting better, but they continue to bear watching.

I would like to talk about four things: the current status of genetic discrimination with respect to insurance and employment, the Genetic Information Nondiscrimination Act (GINA) that appears finally to be on the verge of passage, the future of genetic discrimination beyond the act, and then end by trying to put both the issues of genetic discrimination and the issues of genetic predictive testing in cancer into some broader context.

First, genetic discrimination as we have known it thus far is an interesting, almost contradictory situation, where there is an awful lot of smoke but not much fire. There is great concern and fear about genetic discrimination, but there is very little evidence for the existence of genetic discrimination defined as discrimination against people who are shown to be genetically at risk for diseases, as opposed to people who actually have frank genetic disease. There is discrimination there, but there is very little evidence that there is discrimination against people who are at risk of disease because of their genotypes.

There have been a number of efforts to demonstrate the existence of genetic discrimination. In the early 1990s, there were several articles from people who were determined to find genetic discrimination, and they found a few anecdotal examples of things that might arguably have been genetic discrimination. They were all relying on self-reports of people who had allegedly been discriminated against. They were not followed up very intensively or independently assessed. There were a few better reports as well, but by and large the positive evidence of genetic discrimination was extremely limited.

It is not zero, however. Every once in a while, there is a silly example, Burlington Northern Railway Company being my prime candidate. The company took a group of men who had carpal tunnel disease and decided to get them genetically tested for a syndrome that would have included carpal tunnel disease along with a lot of other things; that syndrome would have kept them from ever working for the railroad. But apart from that example, there has been very little evidence, very few even anecdotal examples, well documented, of genetic discrimination or even attempts at genetic discrimination. Burlington Northern did not even do anything against the

employees they insisted on testing. At least they did not before a stink was raised; who knows what they might have done if allowed to proceed.

I think there are good explanations for why there has been so little genetic discrimination, particularly with respect to the area I think we are most concerned about: health insurance. One is the very structure of our health-care financial system. Most Americans get their health coverage through an employer, either their own, their spouse's, or their parents. Since 1996 and the enactment of HIPAA, and as a cultural matter even before then, employers who provide health insurance have not medically underwritten to any significant extent, except in the very smallest employer context. If you are not medically underwriting, you do not have an opportunity to discriminate among employees, providing some with health insurance, and denying insurance to others who appear to be risky. If there is no medical underwriting going on, there is no possibility for overt and direct genetic discrimination, because there is no decision to be made based on risk factors.

In 1996, HIPAA prohibited employers who are providing group coverage from discriminating based on health risk status. That seems to have coincided with a preexisting cultural norm in most employer-provided groups that has continued, and as a result we do not see health insurance discrimination on the employer side.

The second thing that has happened or has not happened has been that the possibilities for genetic discrimination have turned out to be fewer than we believed in the early 1990s. At that point, as new genetic links to diseases were coming fast and furious, there was an expectation that pretty soon there would be highly penetrant alleles discovered for many common diseases. The discovery of BRCA-1 and BRCA-2 helped feed that belief. The discovery of some of the Alzheimer's genes and the ApoE4 allele helped feed that belief in the early to mid 1990s. But, for the most part, we do not have new major high-risk, high-penetrance alleles associated with common diseases. There are a few, but they are extremely rare. There are more low-risk alleles, things with a penetrance that might take your lifetime risk from 2 percent to 5 percent, or something that has 100 times relative risk. If you are a male and you have a BRCA-2 mutation, you are at 100 times risk of the average male of getting breast cancer, but it still puts you at maybe 1 percent lifetime risk. So we have not discovered the number of powerful genetic associations to disease that I think everybody expected in the early 1990s.

They may still be out there in multigenic forms, in the slot machine version, where we get lemons on three different genes, highly penetrant. But I think part of why there has been less genetic discrimination is that the science has not provided enough opportunities in terms of highly penetrant, high-probability expensive diseases, particularly expensive diseases that are likely to manifest within a time window that is short enough for an insurer to care.

The third reason is that there has been legal intervention. The HIPAA, the Kassebaum-Kennedy bill of 1996, took employer-provided insurance off the map, and that is a huge percentage of insurance. The 30 percent of Americans who get their health care from Medicare or Medicaid are not subject to medical underwriting. The 15 percent of Americans who do not have health coverage are bereft of health coverage more because of income level than any sort of medical underwriting. So the number of people even subject potentially to medical underwriting in the United States is probably down around the 5 to 8 percent of the population that buys individually underwritten coverage.

So, the factors include the structure of the health-care system, the lack of a significant number of strong genetic predictors of disease, some legal interventions at the federal level such as HIPAA, and also at the federal level, some Clinton administration language inserted into an enforcement guidebook of the Equal Employment Opportunity Commission giving an expansive definition of employment discrimination under the Americans with Disabilities Act with respect to discrimination. Then, there have been a plethora of state laws. Roughly 45 states have laws limiting or banning the use of genetic information in health insurance underwriting. Roughly 30 to 35 have laws banning the use of genetic information in employment. So, a number of states have stepped in, even where the federal government has not.

In addition to those factors, if any addition is needed, I think, frankly, the insurance industry has been walking on eggshells about this. They have not been eager to embrace genetic underwriting because they see it is a political loser—the last thing the insurance industry needs is another real political loser. So, to some extent, I think there has been some intentional forbearance for political reasons by the industry from adopting a broad and forthright approach to genetic discrimination, aided of course by the fact that it can only work in the individually underwritten market, and then only in the small number of states that have not otherwise banned it.

Dr. Khleif: What is a broad approach?

Mr. Greely: A company could say, we want everybody to answer questions about whether they have gotten genetic testing; we want people to get genetic tests, and we will not cover you if we think you are at high risk.

Dr. Khleif: As opposed to what, right now?

Mr. Greely: As far as we can tell right now, in the few states that still allow medical underwriting with genetic information in the individual market, a few companies are using it, but not very many even there. There is no evidence of it in other health insurance markets. Nor is there any significant evidence, apart from Burlington Northern, and a very odd case out of Lawrence Livermore Laboratory that I never really understood, of employment discrimination.

So there is really not much evidence this is happening. But there is a fair amount of evidence that people are afraid of it. I think all the genetic counselors around the room, or all the people involved in provision of clinical genetic services, have mentioned in their talks this issue of genetic discrimination as a factor that patients care about. They are worried about losing their insurance or their employment even though there does not seem to be any basis for that fear.

Dr. Greene: The clinical genetics provider community told them to be worried.

Mr. Greely: Because your lawyers advised you to tell them to be worried about that, in large part.

Dr. Greene: And with this becoming the de facto standard of care when counseling for highly penetrant cancer susceptibility, you cannot have a discussion with a patient without warning them that they could be discriminated against in each of these different settings.

Mr. Greely: Which I think began in part because at the time guidelines were being set up in the early 1990s, people expected it, not unreasonably, to turn out to be a bigger problem than it was.

Dr. Weitzel: We were saddled with the Huntington's model.

Dr. Khleif: If you don't disclose on an application that you have a genetic abnormality, could that not be taken against you if you develop the condition?

Mr. Greely: As a good lawyer, the first two words in answering any question are, it depends. With respect to group coverage through an employer, which I assume you probably have, there is an application process that covers you without regard to your health risk. For individual coverage, you can be asked questions, and if you do not answer those questions, they may deny you. And if you answer those questions in a way they do not like, they may deny you. In some 40 states, they cannot ask and act on questions about your genetic information. They can ask if you have had colon cancer, and they can deny you if the answer is yes, but they cannot ask in the vast majority of states if you are at genetic risk for colon cancer. They can ask if you have other conditions that might affect your health. If you say yes, I am a genetic risk for colon cancer, they are not allowed to take that into account in underwriting in those 40-odd states. Every state law is somewhat different; some of them cover individual markets, some of them cover group markets, and some of them cover both. They all have different definitions. But by and large, the states have been pretty strict about this. But there is a lot of fear. The survey evidence on fear is mixed. The anecdotal evidence is quite strong. All the surveys find some evidence of fear. People rank it differently in terms of how important it is to their decisions not to get tested.

Dr. Bach: Just a clarification. That is relevant to health insurance; is that also relevant to life insurance?

Mr. Greely: No, and I will come back to the other insurances. But the ones I think we care most about are health insurance and employment; these are the two areas of genetic discrimination that cause the most concern in the United States. Depending on the survey evidence, somewhere between a third to a half of people will list fear of genetic discrimination as one reason they did not pursue genetic testing.

I am not sure how much credence to give responses like that, in part because I think that for a lot of people, who may have reasons for being nervous about genetic testing, saying I am worried about discrimination is an easy and socially approved answer. Saying I am worried about what my wife will think, or I am worried about the conversation I will have to have with my mother, or I am worried about the possibility of learning that I

am going to die sooner than I thought, those may be harder responses to a survey question than simply to say, yes, I am worried about health insurance discrimination.

Whatever it is, counselors report that there is a significant number of people who are concerned. There is significant concern in the community both that people who should for medical reasons be getting predictive testing are not, and people who you would like to have testing done in research are avoiding it for fear that even with promises of certificates of confidentiality from NIH, there is still the possibility of genetic discrimination.

I have written both in the *Pennsylvania Law Review* in 2001 and then in a perspective in the *New England Journal of Medicine* in September of 2005, that one nice way to deal with the fear is to pass clear broad federal legislation applying to all 50 states that would allow counselors to tell patients they are protected under federal law that provides fairly broad protection. We are I think on the verge of having that happen. The GINA was first introduced by Representative Louise Slaughter in 1995 in the 104th Congress. After languishing in subsequent congresses, now in the 110th, the bill is being taken seriously. It has been approved by the Senate Committee on Health, Education, Labor, and Pensions. It has been approved by the three different House committees that have jurisdiction over it, the Education and Labor Committee, the Energy and Commerce Committee, and the Ways and Means Committee. The last one of those approved it just earlier this week. The three House committees all put in somewhat different amendments, so there is going to be a tricky period of reconciling those amendments inside the House (where the bill passed April 25, 2007), let alone in reconciling them with the Senate bill, which was completely unamended. But that is the legislative norm. When you get to the hearing stage, which this bill had never gotten to before, you get those kinds of detailed markups and amendments.

The GINA would ban genetic discrimination, or discrimination based on genetic information, broadly in health insurance and employment throughout the United States. Its health insurance provisions go to group insurance, individually underwritten insurance, and medigap insurance. It does not affect life, long-term care, or disability insurance, but it covers employers' self-insured plans as well as another major component, HMOs and managed care plans, as well as indemnity plans.

The employment provisions govern all employers. It even governs Congress, the executive branch, and the judicial branch, which Congress does not always do. So it has very broad coverage. It bans in both insurance and

employment the use of genetic information in making decisions, broadly. Genetic information is defined as the results of individual or family genetic tests or family medical history. Personal medical history is not covered, family medical history is. Genetic tests are defined as tests of DNA, RNA, proteins, or metabolites that provide information about a gene, a genetic variation, or mutation, or chromosomal abnormality. Expressly exempted from genetic tests is anything that provides information about sex or age. I have no idea what they are thinking about in terms of the genetics of how old you are.

The act also says that for metabolites and proteins, it does not include a variety of tests that nongenetics people would do. I think that is the cholesterol exception, cholesterol and sugar. So they do not want to say, every time you get a cholesterol test it is a genetic test, although of course it is in a sense. If you have a normal cholesterol, it shows you do not have familial hypercholesterolemia. If you have an LDL level of 800, it shows you do have familial hypercholesterolemia, a genetic disease. Otherwise the law is awfully broad.

An important aspect of GINA, which drives employers crazy, is that it does not preempt state laws. So for those of us in California, our employers and insurers will have to deal both with the federal law, and because California law in some respects is more stringent—and the courts will have a good time figuring out what *stringent* means in some of these cases—California law will also apply. In a state with a less stringent law, the federal law would apply. So the federal law is the minimum standard; states can be more strict if they choose.

The GINA would be enforced by administrative penalties through various cabinet secretaries, notably DHHS, among others, and also enforced on its employment side, not the insurance side, by the same sort of litigation remedies, that is, lawsuits, that apply under the Civil Rights Act of 1964, with the same limitations on damages, punitive damages, and otherwise, something that provokes opposition on grounds that it will lead to more lawsuits. So that is the Genetic Information Nondiscrimination Act of 2007, which I believe is going to become law. Last year the Senate passed an equivalent act 98-0. The White House specifically endorsed last year's bill, not just the concept, which President Bush had endorsed from the time he took office. They have specifically endorsed this year's bill.

There is an antiabortion amendment that is going to get some play on whether or not ex vivo embryos count as people for purposes of the discrimination bill. There is going to be some maneuvering, but it really looks

like it is going to go through this time, which means genetic discrimination should diminish from very small to very, very much smaller. But it also means that counselors and others should be able to tell patients, there is a federal law that is broad and quite clearly protects you against employment discrimination and health insurance discrimination. We cannot promise you that the law will always be obeyed, but there are good penalties to encourage that. So I think to some extent, that should provide a useful solution for many of the concerns.

But there are some future issues here. There are three other forms of insurance—disability insurance, life insurance, and, importantly, long-term care insurance. Neither this bill nor state law, say anything about any of those. The only state laws I know of that talk about life insurance say that you cannot discriminate based on genetic information on life insurance unless it is actuarially justified, which is not terribly consoling to people with a Huntington's disease allele.

Frankly, I do not think that is likely to change much in the United States because we tend to view those forms of insurance more as luxuries and less as the kind of necessity that health insurance has become. Life insurance, particularly high-margin life insurance, is not something that is that common. A lot of people get their life insurance through employers, who again are not allowed to risk rate, to medically underwrite. If you want to go out and buy 5-year term insurance for a 10 million dollar payoff, you are going to get medically underwritten, and I think that is likely to continue.

Disability insurance is a little less certain. There is some federal- and state-mandated disability insurance that will be very attractive to lots of people with these kinds of genetic risks. I think there may be more pressure to make changes there, but most people do not know about it and do not live with disability insurance to the same extent they do with health insurance. Without health insurance, we all know you can quickly become bankrupt. Disability insurance is less of a concern.

I think the sleeper here, although not so much for the cancer community, is long-term care insurance, since the disaster about to confront the American health-care financial system is paying for long-term care. One proposed solution to that is to shift more into long-term care insurance. There is some genetic testing that long-term care insurers and those contemplating buying long-term care insurance would really be interested in, and that is the Alzheimer's test, particularly the ApoE4 allele test. This could be a good predictive test for something that would require long-term care and would represent the kind of adverse selection that insurers like to

complain about. That is plausible in the context of long-term care insurance, which is an expensive investment that very few people are making.

The increasing integration of genetic information in medical practice may pose trickier discrimination issues. The results of genetic tests may define allowable benefits; for example, insurers might decide not to pay for prophylactic bilateral mastectomy in the absence of a positive BRCA test. As far as I can tell, that situation is not covered by the new federal law. It does not prohibit an insurer from conditioning certain benefits on taking a gene test. It prohibits them from demanding a gene test, but does that include conditioning coverage of an intervention absent a good genetic reason documented by a positive test? From the legislative language, it is not clear to me that that is what Congress means. All this assumes that genetic testing will be of value to clinicians and integration will continue, and that will be the case only if clinical decisions are directed by the results of genetic tests. Fitting testing in that context into a nondiscrimination framework may be tricky. I think it can be done, but there will be some problems along the way.

To put all this in a broader context: genetic discrimination against people who have a predictable high risk as a result of their genetic variations for serious disease is certainly not trivial. The problem is not genetic discrimination in insurance, but the 15 percent of our population, the 45 or 46 million Americans who do not have any coverage at all, the 60 or 65 million Americans who will spend some of 2007 with no coverage, and the additional 20 or 30 million Americans who are seriously underinsured. That is a function not of genetics or the laws of nature, it is a function of the fact that we live in the only rich country that doesn't have a civilized health-care financing system.

Interestingly, the British worry about genetic discrimination, not for health insurance because of the National Health Service, but for life insurance. They have a mortgage and banking system that makes loans heavily contingent on getting credit or life insurance which is medically underwritten. So you cannot buy a house unless you get life insurance to pay off the bank if you die before the end of the mortgage. Genetic discrimination is an issue based on the kind of society you live in. For them it is life insurance, for us it is health insurance. Our problem is that we do not cover everybody, and our system is likely to collapse within the next 10 years because costs keep going up too quickly.

So this complicates all of our considerations, everything from how to reimburse genetic counseling to how many new oncologists will be

needed, because it is likely we are going to have a substantially, but at present unknowably, different health-care financing system within the next 10 years. So that is an important uncertainty to keep in mind that will affect everything about genetic testing for cancer, and, of course, everything about the health-care system entirely.

In the broad context of cancer, genetic testing for assessment of cancer risk is currently an interesting but relatively small issue, which is not to minimize the important efforts of the researchers working on it and all the women and men struggling with high risk. If we examine the known genetic variations that are highly correlated with cancer; BRCA-1 and -2, HNPCC, FAP, and many smaller syndromes, and we add all the people up who are likely to be diagnosed with cancer from one of those currently known genetic sources in a year, I doubt that we get to 50,000. There are 1.4 million Americans diagnosed with cancer every year. Roughly 50,000 of them are diagnosed with cancer that is probably the result of what we currently know to be cancer-related genetic variation.

Probably less than one percent, perhaps 0.5 percent, of our population carries genes that we know heavily influence cancer risk. That is 1.5 to 3 million people, and those are not trivial lives in any way. But in the greater world of cancer, that is not a huge number. Twenty percent of our population is walking around with a well-known high cancer risk because they smoke. That is many, many fold the genetic risks we know about. There may be more strong genetic cancer risks out there. We have not found them yet, and they are not going to be easy to find, or we would have found them already. They will probably be multigenic, several different alleles in several different genes, probably combined with some environmental triggers as well. It is hard to know how that is going to sort out, but right now, I would say within the overall scheme of the cancer world, this is an interesting component for research purposes. Identifying the genes tells you something about the natural history and the etiology of the disease that may be useful for the sporadic cases as well. It will be helpful to some, but at present seems unlikely to be a huge driver.

I think we will see more significance in cancer treatment and diagnosis using the genomes not that people are born with, but those of their tumors, to both diagnose cancer by looking for malignant cells or cell surface markers, and then by making decisions about treatment and prognosis based on tumor genetic analysis. My guess is, that will have a bigger effect on cancer in America, at least in a direct way.

Mr. Kean: People move from health insurance plan to plan as they change employers, and a lot of those require some sort of certification regarding preexisting conditions. Are those preexisting definitions included in the discrimination law, either with regard to employment or health insurance?

Mr. Greely: They are covered with respect to employment in the 1996 HIPAA legislation. With respect to employer-provided coverage, genetic risks cannot be preexisting conditions. The HIPAA also limited the total period of time for a preexisting condition exclusion to 18 months. But with employer-provided coverage, genetic risks do not count for that and cannot be used. I do not recall whether the provisions of GINA cover preexisting conditions in the individual market or not.

Just as another example of the complexities you run into, Kaiser Permanente is planning a study of the genetics of 500,000 Kaiser members in northern California. They already have the clinical information on them, and they are going to add genotypes. They need to get an amendment to GINA to do it, because GINA prohibits an HMO from requesting that its members take family genetic tests.

Ms. Javitt: Even if GINA passes, there is still the exclusion of disability and health insurance benefits for military service members if they have a condition that is found to be of genetic origin. My question is, if insurers have basically not been using genetic information to underwrite, why have they opposed GINA for 12 years?

Mr. Greely: I think the answer is complicated. First, the large group insurers, as far as I can tell, did not fight that hard. It was the 800 or so small insurers that usually provide individual coverage in a handful of states who did not want any restrictions on their medical underwriting abilities in the individual market. Even their opposition has cooled significantly as more states have banned it. The real opposition here came from the National Federation of Independent Businesses, the Chamber of Commerce, and other organizations who are worried about the employment law side of it, because they do not want any new federal law that allows employers to be sued by employees for anything.

Dr. Khleif: I have a question that is relevant to the United States and also relevant to the international situation. The FDA reviews studies that are being conducted by domestic and foreign investigators. Some of the foreign

countries do not even have laws about genetic testing and discrimination. So from a bioethical perspective, what are the things that need to be taken into consideration regarding those issues? What we look for is whether the person is going to be counseled properly or not. But we do not examine the protections in that particular region of the world for the individually identifiable information that is needed for the scientific goals of the study.

Mr. Greely: That is an interesting question, and not one that I have really given thought to. I would think that if you wanted to take a step beyond proper informed consent and protection against research risks, you would look at the structure of the health insurance system. In the developed world, that is not going to be a problem, because there is universal coverage. In low-income countries, it is not going to be a problem because almost all the population is not going to have coverage anyway. In middle-income countries or in the case of rich or middle-class people in the poor world, you might inquire what the structure of the health-care financing system is in that country and whether there are protections against genetic discrimination.

Dr. Khleif: I wonder if there are some guidelines being developed for genetic testing and discrimination. This is an issue that is going to be more and more significant.

Mr. Greely: I agree. I think that is interesting and might be a worth pursuing. It is not going to be so much a problem with Europe or China or Korea, but I have no idea what the health-care financing system's position on genetic discrimination is in India or Thailand or Brazil.

Dr. Greene: I wonder about the numbers you suggested for carriers with high-penetrance mutations in the general population. I cannot say that I know off the top of my head what the correct number is, but when you consider BRCA-1 and -2, for example, people argue about what the prevalence of deleterious mutations is in the general population; one in 500 seems like a reasonable place to start.

Mr. Greely: That is actually what I did. I started with BRCA-1 and -2 at 0.2 percent. I added HNPCC and FAP, probably another 0.2 percent or so. After that, the pickings get slim. There is a little bit of melanoma. There are things such as Li-Fraumeni, a very small number of people. So I think

the wiggle room between 0.5 and 1.0 percent is probably fair from what we know today. I agree that it may not be fair for what we will know in 10 years. It would have been nice if I had gone through and found all the latest numbers on all the syndromes, but from work I have done in the past, those numbers are not very solid, anyway.

Dr. Weitzel: Part of the problem is that because of all the phenocopies, we are looking at only 20 percent of the people we select to test being true positives. We cannot select better than that because breast cancer phenocopies are everywhere. It does not diminish the need for genetic testing, because with testing we identify those few that do have very high risk. Proportionately, they have a much higher impact on the health system, because if they go on without screening, they will develop disease at very highly penetrant rates.

Mr. Greely: I do not disagree with that. If you take as a high estimate 10 percent of breast cancer diagnoses in women with a BRCA-1 or BRCA-2 mutation, that is about 21,000 women a year. If you do 1 percent with colon cancer, it is about 1,500 a year out of 148, 000 new cases. Those are the two most important ones among the cancer risk syndromes, and you are up to 23,000 people out of 1.4 million total new cancer diagnoses. So it is not to say they are not important, but they are not a huge percentage of the cancer burden as far as we know.

Dr. Greene: We may end up testing 20 percent of those new cases in order to find the 5 percent, let's say, that are true positive. So the application of the science allows one to identify the patients for whom genetic testing will convey the greatest benefit.

Mr. Greely: Although, I think we are headed to a situation where with new technology and the expiration of the Myriad patent in 2013, we test just about everybody at low cost within the next 10 to 15 years. So, we will have population-wide numbers as well and be able to do disease prediction, and only test people who are at high risk.

Dr. Harold Moses, Director Emeritus, Vanderbilt-Ingram Cancer Center and Chair, National Cancer Policy Forum: I would like to thank all the speakers. It has been very informative. I would like to thank all the people who asked questions and added to the discussion and to what I think has been a very productive workshop.

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Appendix

Workshop Agenda

Institute of Medicine
National Cancer Policy Forum
The Keck Center of the National Academies
500 5th Street, NW
Keck 201
Washington, D.C. 20001
March 30, 2007

6:30 pm	*Thursday, March 29, 2007 at the Henley Park Hotel* Dinner
8:00 am	*Friday, March 30, 2007 at the Keck Center, Room 101* Continental Breakfast
8:30 am	Welcome, Opening Remarks, Approval of Minutes, Forum Updates, Other Business *Harold Moses*
9:15 am	The Promise and Pitfalls of Cancer-Related Genetic Counseling and Testing *Patricia A. Ganz, UCLA*

9:55 am Current and Future Demand for Cancer-Related Genetic Counseling and Testing Services
Robin Bennett, Senior Genetic Counselor, Clinic Manager, University of Washington Medical Center

10:35 am Break

10:50 am Implications of Home Tests and Direct to Consumer Advertising
Gail Javitt, Law and Policy Director, Genetics and Public Policy Center, Johns Hopkins University

11:30 am Delivery and Research Issues-Healthcare Provider Supply and Preparedness
Mark H. Greene, Chief, Clinical Genetics Branch, DCEG, NCI

12:10 pm Lunch

1:00 pm Delivery and Research Issues-Providing Community-Based Services
Jeff Weitzel, Director, Department of Clinical Cancer Genetics, City of Hope Cancer Center

1:40 pm Delivery and Research Issues-Reaching Underserved Groups
Chanita Hughes-Halbert, Director, Community and Minority Cancer Control Program, University of Pennsylvania

2:20 pm Reimbursement Issues
Debra Lochner Doyle, Manager, Genetic Services Section, Washington State Department of Health

3:00 pm Break

3:15 pm Psychological Impact on Patients and Families
Marc Schwartz, Associate Professor of Oncology, Co-Director, Cancer Control, Georgetown University

3:55 pm Implications for Access to Health and Life Insurance
Henry T. Greely, Professor Law and Genetics, Stanford Center for Biomedical Ethics, Stanford University

4:35 pm Concluding Remarks and Adjourn
Harold Moses