Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development: Workshop Summary

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Steve Olson and Adam Berger, Rapporteurs; Roundtable on Translating Genomic-Based Research on Health; Institute of Medicine

ESTABLISHING PRECOMPETITIVE COLLABORATIONS TO STIMULATE GENOMICS-DRIVEN PRODUCT DEVELOPMENT

W O R K S H O P S U M M A R Y

Steve Olson and Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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

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

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth**.

Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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Abbreviations and Acronyms

CaHUB	Cancer Human Biobank
CEO	chief executive officer
CHEP	Community Health Engagement Program (Indiana)
CTSA	Clinical, Translational, and Science Awards
CTSI	Indiana Clinical and Translational Sciences Institute
DMPK	drug metabolism and pharmacokinetics
FDA	Food and Drug Administration
IMI	Innovative Medicines Initiative
IOM	Institute of Medicine
IP	intellectual property
NCI	National Cancer Institute
NIH	National Institutes of Health
PI	principal investigator
R&D	research and development
UCSF	University of California, San Francisco
UDBN	UK DNA Banking Network

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Introduction

Key Points Raised by Speakers

- Precompetitive collaboration needs to expand substantially to overcome barriers in drug development.
- Collaborative efforts could produce rapid advances in a wide spectrum of activities now conducted largely by individual companies working separately.
- Collaborations are successful when all of the participants involved benefit.
- Millions of biospecimens linked to phenotypic data exist in the United States, but biobanks are fragmented and isolated.

The field of genomics has the potential to revolutionize our interactions with the health care system, from increasing awareness of our risk for common diseases to individualized drug design. However, even with the significant increase in basic discoveries since the sequencing of the human genome 10 years ago, there has been a troubling paucity of new disease therapeutics, diagnostics, and preventive measures based on these discoveries.

This gap between discovery and application results in part from the complexity of human biology and disease processes. The growth of large databases in genomics, proteomics, metabolomics, and other dimensions of biological systems has helped reveal the inherent complexities of mul-

tiple gene-environment interactions, incomplete gene penetrance, and the dynamics of biological networks. However this gap also results from a lack of funding to substantiate the clinical relevance of basic discoveries and the increasing time and cost required to convert discoveries into commercial applications.

One way to bridge this growing divide in the translational pathway is through partnerships that distribute the risks involved in research and development (R&D) among multiple parties in a precompetitive manner. Industry, academia, and government all hold tools, knowledge, and biological materials that could be used collaboratively to speed the development of new drugs, diagnostics, and preventive measures. In particular, the sharing of biological specimens (biospecimens) and the data derived from those biospecimens through large-scale precompetitive collaborations could offer substantial benefits to all parties involved and the public at large.

However, numerous issues such as intellectual property (IP) protections and funding can be cumbersome or completely inhibitory to establishing collaborative ventures and must be overcome to facilitate this process and realize the potentially immense benefits. To explore these issues and develop potential solutions, the Roundtable on Translating Genomic-Based Research for Health held a workshop on July 22, 2010, entitled "Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development" (see Appendix A for the full agenda). Representatives of government, industry, academia, and nonprofit organizations participated. Speakers and workshop participants sought to:

- Examine specific examples from other industries that have engaged in precompetitive collaborations;
- Identify how the best practices from other successful collaborations can be applied to genomics;
- Clarify the rules of engagement for each stakeholder that would allow for genomics-based collaboration; and
- Elucidate a conceptual framework for the precompetitive sharing of biological resources from many different stakeholders—academia, industry, government, and others.

While the workshop had a particular focus on stored biospecimens and the data derived from those samples, most of the observations could apply much more broadly in the development of drugs, diagnostics, and preventive measures in biomedicine. However, the goal of the workshop was not to solve the problems surrounding the establishment of precompetitive collaborations but rather to foster discussions that could clarify the issues and identify potential solutions.

EXPANDED USE OF PRECOMPETITIVE COLLABORATIONS

Recent years have seen a substantial expansion in the number of precompetitive, collaborative, multistakeholder consortia or relationships that have been established to address bottlenecks within the drug development process. Several examples of these include the Innovative Medicines Initiative in Europe, which is focused on bottlenecks in safety, efficacy, and preclinical toxicity; the Biomarkers Consortium, which is developing predictive biomarkers for such diseases as breast cancer, sarcopenia, and atherosclerosis; the Predictive Safety Testing Consortium, which is looking at liver, muscle, vascular, and renal diseases and carcinogenicity; and the Coalition Against Major Diseases, which is developing a shared Alzheimer's database and quantitative disease models.

However, these collaborative arrangements, many of which are relatively new, fall far short of meeting current needs, said Geoff Ginsburg, professor of medicine and director of the Center for Genomic Medicine at Duke University, during his introductory remarks. Approval rates for new molecular entities in the pharmaceutical industry have been flat or declining over the past two decades (Booth and Zemmel, 2004; CBO, 2009). The return on investment has dropped precipitously for companies seeking to develop new drugs (Figure 1-1) and the problem of declining returns for increasing effort cannot be solved by any one organization working alone, suggested Ginsburg. Companies, government, and academic researchers need to combine their complementary skills and resources if they are to take advantage of the wealth of new information and knowledge made available through genomics-based research.

A wide variety of topics and tools are potential targets for precompetitive collaboration according to Ginsburg, including biospecimens, model systems, drug targets, probes, clinical and molecular data, preclinical models, software, and clinical trials data.

IDENTIFYING NEW APPROACHES TO PRECOMPETITIVE COLLABORATION

Stephen Friend, president and chief executive officer (CEO) of Sage Bionetworks, summarized the key points from an earlier Institute of Medicine (IOM) workshop on precompetitive collaboration in oncology research as background for the discussion (IOM, 2010).

For collaborations to succeed, related Friend, people need to work together in very different ways than they have in the past. Partners have to be able to share not just information but materials and personnel. They need to be willing to develop innovative tools, activities, and infrastructures for collaboration. Taking these steps requires a commitment from key

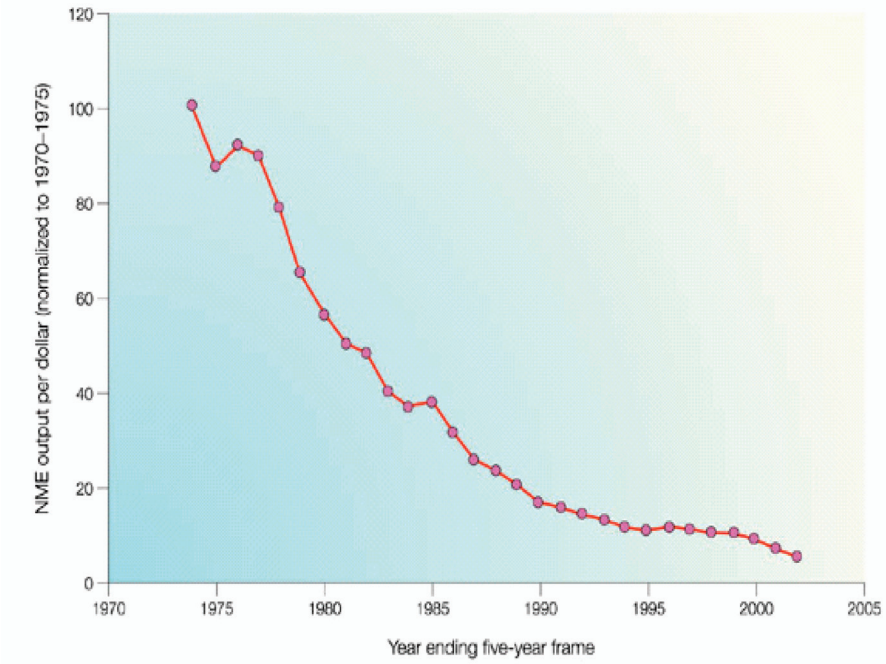

FIGURE 1-1 Normalized new molecular entity output per dollar expended.
SOURCE: Booth and Zemmel, *Nature Reviews in Drug Discovery*, 2004.

leaders. "You can dream all you want about how beautiful it is to have public-private partnerships, but if you don't have leaders who are willing to build those tools and an infrastructure that allows sharing, it's very hard," said Friend.

Successful collaborations may require particular inputs, recounted Friend. One likely element of success is a neutral convener that can combine the relevant stakeholder perspectives and provide a legal safe harbor for collaboration. It does not need to be government, "it doesn't need to be a nonprofit, it doesn't need to be industry," said Friend. "It has to be someone who actually can look at what are the consequences for the many groups that are coming together."

Successful collaborations also can require governance structures that allow collaborators to develop strategies that are economically and intellectually sustainable. Sufficient incentives may have to be put in place to overcome existing incentives and to motivate the creation of policies that reward the development of an infrastructure for effective collaboration. These incentives can take the form of support for process, participation, or

reporting; support for results; or support for data exchange and meaningful analysis. As Garry Neil, corporate vice president for Johnson & Johnson, pointed out, building a robust national infrastructure to conduct and disseminate the data from clinical trials could bring tremendous cost savings to industry, government, and consumers.

Finally, effective collaborations may require the identification and prioritization of "bottleneck" knowledge gaps that can be addressed more effectively through precompetitive collaboration, the development of information "utilities" such as data standards and infrastructures, less regulatory uncertainty, and more head-to-head evaluations of collaborative models to identify key features and best practices. For example, Friend suggested that Clinical and Translational Science Awards could provide a mechanism for greater collaboration, as the institutions that have received these awards are working on ways to share data that could provide a template for many other kinds of partnerships.

In some collaborations, the use of open source principles can enable distributed innovation. "Tasks do not have to be built out of centralized efforts run from a single point," said Friend. "The real power in the twenty-first century will come from distributing tasks." Open source collaborations can require novel intellectual property provisions, a resource model that can support such work, and the establishment of conditions for entering, exiting, and ending a collaborative effort.

Another possible approach, said Friend, is the use of prizes to motivate collaborative research. "You do not have to have two years of going through a grant review process and then pay people to do certain tasks. Prizes [offer] a much more effective way to fund things." Any organization could use such a mechanism, said Friend, including the National Institutes of Health (NIH). He contended that "the sole emphasis on the grant structure the way it is misses an opportunity to have prizes drive some of those opportunities." Friend also suggested that perhaps one-third of R01 funds could be distributed in different ways than through traditional grants. For example, large, infrastructure-driven projects could produce faster results for patients and reduce repetitive work. "I think it's going to go in that direction . . . as the government has less money," said Friend. Though he added that he did not know whether alternative funding mechanisms would be easy to institute, he said they are "worth considering."

In addition, patients can drive collaborations. For example, patients can organize initiatives to collect samples associated with phenotypes and share those samples and information widely with researchers. Patients are extremely aware of what their diseases are doing to them, said Friend, and they can gather information about their diseases that would be impossible for physicians to gather.

Importantly, summarized Friend, all the participants in a collaboration

need to benefit. Patients need to have an opportunity to contribute to the development of more effective and ultimately personalized treatments. FDA needs to receive data and other input for evidence-based regulatory policy. Pharmaceutical companies need to see opportunities for more efficient drug development and approval. The device industry needs to benefit from larger markets and less risk. Academic researchers need to receive better clinical data and be able to work toward more effective treatments. "Altruism is a great philosophical concept, but someone's got to feel there's something in it for them," said Friend.

Friend ended his talk by discussing the concept of "extending the spectrum" of precompetitive biomedical research. The sharing of non-compound data and disease models occupies the middle of the spectrum. However, the middle of the spectrum is surrounded by many other activities that can be done collaboratively, including sharing analytical tools, revenue, scientists, consultants, clinical compound data, toxicity data, and compounds themselves. "We should mark our progress over time, where we are along that spectrum," Friend said.

Three themes to keep in mind in considering the precompetitive space, said Friend, are the following:

- Diverse approaches are needed for diverse goals.
- The cultural barriers are often higher than the technical barriers.
- Collaboration requires neutral and well-funded coordination with incentives for all participants.

THE POTENTIAL FOR PRECOMPETITIVE SHARING OF BIOBANKED SPECIMENS

As an example of an area where collaboration could be of substantial benefit to all parties, biospecimens represent a significant untapped resource of genetic and genomic information that can be used for target discovery, target validation, biomarkers for decision making, pharmacodynamics, pharmacogenomics, predisposition, prognosis, efficacy and monitoring, and replication.

Much more widespread use of biospecimens and their derived data could benefit multiple stakeholders, according to Ginsburg. Patients could receive better treatments, diagnostics, and use of their samples and data. Regulatory bodies could create and streamline standards for policy making. Pharmaceutical companies could use biomarkers to investigate drug targets, biological pathways, and disease mechanisms, leading to more efficient drug discovery and development, targeted therapies, and faster and less costly innovation cycles. Diagnostic companies could expand their portfolio of potential diagnostic products and reduce the risks in the discovery process.

Universities and academic health systems would have access to new data, funding, and hypotheses. Also, Ginsburg said, the efforts of all of these stakeholders would produce benefits for the broader society.

As an example of potential benefits, Ginsburg cited a research project by David Goldstein and John McHutchison at Duke University who used data from a clinical trial to discover a genetic variant that has a dramatic effect on the efficacy of a drug combination in patients with hepatitis C (Ge et al., 2009). In a second study, Goldstein, McHutchison, and their colleagues used access to six cohorts of hepatitis C patients around the world to demonstrate that the genetic variant could predict rapid clearance of the virus. Within months, the company LabCorp announced the availability of a genotype test to support individualized treatment decisions for patients with hepatitis C infection. "This is an example of access to large clinical data sets, applying genomic technologies, and, at least in my experience, one of the most rapid translations to a product that's on the market," said Ginsburg.

More than 300 million biospecimens are currently stored in the United

TABLE 1-1 Biospecimen Storage in the United States, 1999

Type of Repository	No. of Cases	No. of Specimens	Cases per Year
Large tissue banks, repositories, and core facilities	>2.8 million	119.6 million	390,790
Longitudinal studies	>340,088	508,088	
Pathology specimens	>160 million	>160 million	>8 million
Newborn screening laboratories	>13.5 million	>13.5 million	<10,000 to >50,000
Forensic DNA banks	1.4 million	1.4 million	
Sperm, ovum, and embryo banks	>>200	>9,900	>9,900
Umbilical cord blood banks	>18,300	>18,300	
Organ banks		>75,500	>75,500
Blood banks		~12 million	~12 million
Total	>178 million	>307.1 million	>20.5 million

SOURCE: E. Eiserman and S. Haga, *RAND Handbook on Human Tissue Sources: A National Resource of Human Tissue Samples*, MR9540ST, 1999.

States (Eiseman and Haga, 1999) (Table 1-1) and an informal survey Ginsburg conducted among colleagues before the workshop found that one major pharmaceutical company enrolls about 32,000 patients per year in clinical trials and an academic health center reported 45,000 patients in trials and registries in 2010, although each collects specimens from only a fraction of those patients. Additionally, a recent survey by Willett and colleagues (2007) revealed that roughly a million specimens are associated with large U.S. cohort studies for which clinical data exist. Based on these surveys, Ginsburg estimates that millions of biospecimens in the United States are linked to at least some phenotypic information, but access to these samples is limited, and the biobanks tend to be fragmented and isolated. "Samples are widely distributed and nobody actually knows where they are [and], for a lot of them, what they are," said Ginsburg, "with limited access even among investigators in the academic health center enterprise." Thus, immense benefit could be realized if a framework were developed that would allow these samples to be pooled together and shared precompetitively in a collaborative venture.

2

A Lesson About Precompetitive Collaboration

Key Points Raised by the Speaker

- The U.S. semiconductor manufacturing industry successfully met a challenge from foreign manufacturers in part through the formation of SEMATECH, an industry-led joint venture to work together on the technologies underlying semiconductor manufacturing.
- Keys to the success of SEMATECH were stable funding, ties between industry and academia, and involving the best people in the collaboration.
- The pharmaceutical industry can learn from and apply the best practices that other industries developed when faced with a similar need to foster precompetitive R&D.

THE SEMATECH EXPERIENCE

William Spencer, the chairman emeritus of SEMATECH, described how the semiconductor manufacturing industry responded when it faced a challenge that required collaborative efforts among competing companies.

In 2010 the U.S. semiconductor industry should make about $300 billion in sales, said Spencer, while supporting an electronics industry that does about a trillion and a half dollars in business per year. "If you count the number of transistors you have on yourself right now—with your cell phone, your pager, your watch, the key to your car, some of your credit

cards, and if you have a laptop with a couple of memory sticks in it—you've probably got 10 [billion] to 100 billion of those little buggers on your body or in your purse right now. That's close to the number of cells that you have in your body, not quite the number, but the transistors are multiplying faster," said Spencer.

The transistor was invented by two scientists at Bell Laboratories in 1947 (Brinkman, 1997), and about a decade later two separate companies, working independently, discovered how to combine many transistors onto a single chip of silicon. This started the semiconductor industry whose growth, according to Spencer, took off in the 1960s when the U.S. government chose to use integrated circuits in military systems, including the Minuteman missile. At that time, the semiconductor industry was small—perhaps just a billion dollars—and the Department of Defense accounted for about half of those sales.

By the mid-1970s, the industry had grown to approximately $5 billion in sales, and integrated circuits were being used much more widely. At that time, the United States owned about two-thirds of the world market in semiconductor chips and almost 100 percent of the market in the complex equipment used to manufacture those chips. However, other countries, particularly Japan, saw an advantage in semiconductor manufacturing and in 1975 started a cooperative effort between industry and government to boost the industry (Sakakibara, 1993).

According to Spencer, by 1985, the United States had lost market leadership in semiconductor manufacturing. At that point, it cost about a billion dollars to build a new factory to make semiconductor chips, and the equipment for a factory might cost several hundred million dollars. If a company made a mistake in building a plant, failure represented a huge cost, but if a company chose not to invest in plants it lost market share and future revenue.

The Department of Defense did not think that buying semiconductor chips from outside the United States was a good idea due to national security concerns about reliable and secure sources of chips, according to Spencer. This concern contributed to the formation of SEMATECH—an acronym for semiconductor manufacturing technology—as a cooperative effort between the federal government and the U.S. semiconductor industry.[1] SEMATECH initially had a budget of about $200 million, representing about 75 percent of the U.S. semiconductor industry, with a little less than 50 percent of that amount coming from the federal government and the rest from private industry (CBO, 1990).

[1] The Bayh-Dole Act, enacted on December 12, 1980, created uniform patent policies regarding federally funded research. This legislation also provided the legal framework under which SEMATECH was formed in 1987.

At first, former competitors working together at SEMATECH were wary. Spencer recalled an engineer telling him that her company had told her to "listen, don't talk, and lock your file cabinet." However, the work at SEMATECH quickly revealed the advantages of cooperation. The problems being tackled at SEMATECH were being worked on independently by different companies. "By getting together, those problems could be solved jointly, saving a great deal of time and a great deal of money," observed Spencer.

By the mid-1990s, the United States had regained its market leadership in the semiconductor industry. There were many reasons for that, Spencer acknowledged, including changes in tariffs, exchange rates, trade barriers, and technologies, but SEMATECH clearly played a role.

LESSONS FROM SEMATECH

Spencer highlighted several key points from his experience at SEMATECH that were necessary for its success. First, it is important to have stable funding for such a venture. Funding for SEMATECH was provided through regular federal appropriations and industry. Federal support for SEMATECH was in the President's budget that was submitted each year. Inclusion in the President's budget is critical, he said, to avoid budget battles within each agency.

Second, according to Spencer, industry-led collaborations need ties to universities to draw on the creative ferment of academia. A close association is advantageous for the initiation of cooperative efforts with faculty who are already experts in disparate fields. Additionally, it allows for identification of outstanding graduates who could work directly for SEMATECH or one of the member companies. Spencer noted that while a consortium might be located close to a specific university, it is also important to establish relationships with every other university where there is an overlapping common interest.

Most important, said Spencer, such ventures need to attract the best people to be successful. To do that, those people need to see a way to enhance their careers. Companies needed to be convinced that they should send their best people to SEMATECH and that once those individuals returned to the company, they should receive some kind of promotion, bonus, or recognition. If companies did not do that, their best people tended to leave for other companies, since the best people in the industry were widely recognized and sought by competing companies. "They could send them to SEMATECH and they'd return a lot smarter and a lot more knowledgeable than they were when they left," said Spencer.

3

Requisites for Successful Precompetitive Collaboration

Key Points Raised by Speakers

- Industry's perceptions of the domain of precompetitive research have been expanding, though internal tensions can point to areas of ambiguity and the boundary can vary among companies and academic researchers.
- Universities and other organizations need to take advantage of multiple opportunities to change traditional practices.
- New ways of measuring achievement would provide incentives for more researchers to participate in precompetitive collaborations.

REQUISITES FROM THE PHARMACEUTICAL INDUSTRY

Over the last five years, Pfizer has become involved with a number of precompetitive consortia, said Aidan Power, vice president and global head of Molecular Medicine for Pfizer. "We're building on a repertoire of experience within the industry of consortia that have been developed over the past four or five years. The questions for us now are, what have we learned from that, and what can we do better?"

Several issues need to be resolved in order to establish a collaborative consortia from the pharmaceutical company perspective. A major challenge is defining the domain of precompetitive research. The basic biology, the understanding of disease, biomarkers of prognosis, and even drug responses

all can be areas of precompetitive R&D, Power said. Pharmaceutical companies have recognized that they cannot develop a full understanding of these different facets of drug development on their own. Instead, related Power, they need to leverage the capabilities of many organizations, including government and academia. A few years ago, Pfizer would have considered the chemistry, the execution, and the quality of products to fall into the competitive arena, but even these areas may not be inviolate. Proposals to establish consortia that cover at least part of this territory have generated interest from pharmaceutical companies. However, some stakeholders may still view this research as strictly competitive. The line may be drawn differently between academia, diagnostic companies, and pharmaceutical companies, said Power.

Setting up consortia can also be labor intensive. As Power pointed out, "The political science precedes the real science." Consortia such as the Biomarkers Consortium and the Serious Adverse Events Consortium took at least 18 months to get off the ground. To establish a contract, the views of multiple parties need to be reconciled.

Internal issues can illustrate inconsistencies regarding, for example, intellectual property. The legal departments of pharmaceutical companies are changing their definitions of what needs to be patented, but only under pressure. "It used to be the case that we patented everything. But establishing patents and continuing to uphold them is a very expensive business, and we can't afford to do that anymore. . . . We are beginning to operate in a space that would have been inconceivable to us a few years ago."

Establishing consortia also raises issues about decision-making and participation criteria. For example, asked Power, what happens when new members come into a consortium? What do they receive? What if their support is not equivalent to the other members? How can rules governing such events be established in advance?

A good example of the potential for collaboration involves the samples collected in clinical trials. If these samples and their related data could be pooled across companies and with academia, intellectual capabilities could be increased and very good research could be done. Another possibility for collaborative research, said Power, would be to look at whether compounds developed for one purpose have valuable uses with other diseases or disorders, since the pharmaceutical industry needs to improve its ability to identify effective compounds that target the appropriate biological mechanisms.

Regarding the future, the precompetitive space is likely to continue to expand at the cost of internal development, Power said, as Pfizer has decided to reduce internal infrastructure costs to free up funds to invest in these ventures. Pharmaceutical companies remain under great pressure to come up with new products, and fewer are becoming available from biotechnology companies than had been anticipated. Pharmaceutical com-

panies will continue to emphasize the establishment of consortia, concluded Power, developing ways to allow access to data, sending their best people to participate, driving to publish findings from precompetitive collaborations, developing new provisions for intellectual property, and taking advantage of government incentives for precompetitive research.

REQUISITES FROM DIAGNOSTIC COMPANIES

LabCorp is one of the two large diagnostic companies in the United States, said Marcia Eisenberg, a senior vice president in the company. It has more than 27,000 employees and more than 1,500 patient service centers. It reports more than 1.2 million results daily from 400,000 specimens collected from 220,000 clients. Its mission is to provide a broad range of clinical and anatomic pathology services to aid clinicians in the diagnosis, monitoring, prediction, and prevention of disease. About 70 percent of its tests are ordered electronically, and 90 percent of results are delivered electronically.

Diagnostic companies interact with many different groups and organizations—physicians, insurance companies, pharmaceutical companies, and government agencies. However, they tend not to interact much with each other. The most prominent form of interaction in the past few years has been the buying and selling of diagnostic companies, with the total number of companies dwindling in the current economic downturn.

Diagnostic labs are required to cooperate in a number of areas to ensure that analysis and reporting are standardized, Eisenberg pointed out. They use many of the same positive and negative controls, share reporting elements and formats, have standards for adverse events and corrective actions, use the same nomenclature, participate in health information exchange systems within the labs and within the systems connected to the labs, and so on. In many of these cases, cooperation is required by the government, done to enhance patient care, or expected as part of the ethos of scientific work. LabCorp, however, has rarely, if ever, engaged in collaborative initiatives of its own accord.

Several areas could easily be collaborative between diagnostic companies, according to Eisenberg. Companies could more widely share the details of their internal quality systems, enhance standards for reporting adverse events and corrective actions, standardize the reporting and handling of incidental findings, and publicize best and less-than-best practices. These could serve as easily achievable first steps to enhance collaborative efforts.

However, more difficult challenges would be posed by those practices that are "the heart of what makes us competitively different," said Eisenberg. These include standard operating procedures, interpretation

formats, the formatting and standards for orders and requisitions, and the formatting and procedures for notifications. "Those are things that are held quite confidentially." Eisenberg noted that she personally saw no problem with sharing much information related to standard operating procedures, but her "legal and compliance group would see it otherwise." It may also be difficult for diagnostics companies to be fully transparent on their assays "because this is how we're competitive and [how] we [can] separate from each other." The technologies used by companies are often the same, making the procedures the distinguishing factor among companies.

In general, tasks and technologies that make these companies money may be difficult to share, according to Eisenberg, while regulatory actions and the involvement of certification organizations could be a force for greater industry-industry collaboration.

REQUISITES FROM ACADEMIA

The academic environment is very heterogeneous, said Neal Cohen, professor of anesthesia and medicine and vice dean at the University of California, San Francisco (UCSF), School of Medicine. It encompasses undergraduate and graduate education and a diverse faculty with disparate goals and measures of success. The basic scientist has to publish, the clinician is promoted based on doing good clinical work and disseminating that knowledge, and the clinician scientist is trying to expand the translation of science to patients and expand patient care beyond the institution. As an example of the tensions that these different success measures can create, Cohen cited the merger of the UCSF and Stanford hospitals in the 1990s. "That merger lasted six years: two years for the engagement, two years for the marriage, [and] two years for the divorce."

The traditional model is no longer adequate, said Cohen. The government and the public believe that science can move faster and provide cures for diseases that have largely defied intervention in the past. Moreover, federal funding for research comes at a cost, related Cohen. Most faculty who have NIH funding, when they submit a proposal, are actually working on their next proposal and have already well articulated the science they are espousing, "because the only way to be successful is to demonstrate that you've been successful." The result is that creativity and innovation are undermined. "These models [for success] aren't sufficient any longer. We clearly need more complex methodology and clinically important questions answered. We need to think about ways to move forward," urged Cohen.

Collaborations between academia and industry are thus critical to the success of the academic community, Cohen said, and he expressed confidence that it is possible to cooperate while dealing with the conflicts that arise. "When we're talking about collaborations . . . we shouldn't be think-

ing in the same terms, or with the same definition of precompetitive as we mean within industry, because precompetitive has a very different meaning [in academia]. We need to move beyond it and recognize how we can work collaboratively in a way that fulfills the goals and needs and incentives for academicians and the incentives for industry."

Several issues within the culture of academia are currently limiting the value that is placed on industry relationships. Intellectual autonomy is a very significant issue in academia, according to Cohen. "Compartmentalization of knowledge [and] the merit and promotion processes need to be reevaluated. If we, as a group of institutions, got together and defined ways that the promotions committees could evaluate interdisciplinary, multidisciplinary activities, it would be very helpful." The 37th of 47 authors on a paper may have been critical to its success or may simply have provided some patients. "Unless the individual is able to articulate [his or her] role, validate [that] role, and talk about how important [it] is, it will be difficult to move the agenda." Cohen suggested that databases of participation could be used to evaluate performance.

University policies and procedures need to be devised in such a way as to enable the development of relationships rather than placing restrictions on academic faculty who want to enter into these collaborations, according to Cohen. Contract negotiations, technology transfer, and economic autonomy need to be reexamined. Interdisciplinary research programs within or among institutions also need to be valued appropriately because currently, said Cohen, "even though many of our faculty have very strong relationships, they're competing for first authorship rather than competing for the best science."

Strategic visions and scientific strategies need to be developed to allow individual scientific collaborations to advance more rapidly, according to Cohen. Potential collaborators throughout the academic community need to be identified, including among basic and clinician scientists, he continued. Clinicians can provide keys to breakthrough technologies by understanding the mechanisms of disease, monitoring individual responses to and compliance with therapies, and serving as a source for patient cohorts and biological specimens. To facilitate this type of collaboration, UCSF, for example, has developed a searchable website that points to research projects and collaborations by disease. This enables people to talk together from an epidemiological basis, a basic science basis, and a clinical basis. "Getting those people to talk together and understand where there are opportunities to work with industry will be critical," said Cohen. Such a database could also provide the opportunity and infrastructure for students and residents to identify potential mentors, concluded Cohen, since the training of the next generation of researchers and clinicians also needs to emphasize the importance of these relationships.

The Clinical and Translation Science Awards program has provided a better sense of what people are doing. This model also provides a way of thinking differently about engaging the community at large and building relationships among community providers, industry, and clinicians, Cohen pointed out. "Academia needs to emphasize that relationships are critical, that we are managing them responsibly, that we are addressing the fundamental scientific basis of the relationship, and that we are evaluating the outcomes appropriately."

An Industry-Academic Framework

Cohen suggested a potential framework for establishing industry-academic collaborations. An oversight structure needs to be defined that promotes exchange of knowledge, he related. For example, a strategic planning board could clearly define goals and objectives. A coordinating committee could identify potential collaborative partnerships and coordinate their activities, identify and leverage campus and investigator expertise, and manage databases and specimen banks. An advisory board could evaluate strategies, provide oversight, and manage conflict-of-interest issues (Figure 3-1).

Industry is also diverse, Cohen emphasized. There are opportunities to develop nonexclusive consortia and networks with academics in what industry defines as precompetitive areas and to create incubators within academic health systems. These relationships need to be managed as a port-

FIGURE 3-1 Model for industry-academic collaboration.
SOURCE: Cohen, IOM workshop presentation on July 22, 2010.

folio, said Cohen, with key partners identified. Master agreements need to be negotiated, so that delays can be minimized for individual agreements.

Risk and the Academic Enterprise

Stephen Eck, vice president for Translational Medicine and Pharmacogenomics at Eli Lilly and Company, observed that if academic investigators, and those who review their grants, are risk averse, industry is much more risk averse, since more is at stake. "How does precompetitive collaboration get those two sectors to actually work on the risky stuff that has potentially very high payoff?"

Investigators are not risk averse, replied Cohen, though they want publications. Rather, the universities are risk averse, especially regarding their public image. "They are very careful to control their imprints, their name, and their position in society."

Individual investigators vary in the amount of risk they are willing to assume. Some very entrepreneurial basic scientists are always on the cutting edge, despite the difficulties this can raise in getting grants. For example, Stanley Prusiner, who won a Nobel Prize, had great difficulties getting government funding and was supported by industry and donors to advance his science, said Cohen. "He followed his pursuit because he had passion and he was willing to take the risks, and he found people who would help support him, but he could have fallen off the edge of a cliff easily and never completed his research."

4

Frameworks for Collaboration

Key Points Raised by Speakers

- NIH can function as a valuable partner for drug development through its support of standardization, integration, and sharing of resources.
- The desire to protect intellectual property can be an obstacle in establishing precompetitive collaborations.
- Newer models of how science is funded and rewarded offer a way to recognize the contributions of distributed networks of researchers.

PUBLIC–PRIVATE PARTNERSHIPS WITH NIH OR GOVERNMENT

The mission of the NIH, as steward of medical and behavioral research for the nation, is to advance "science in pursuit of fundamental knowledge about the nature and behavior of living systems . . . and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability." Those two separate missions, though closely related, have differing implications for the development of partnerships, said Thomas Insel, the director of the National Institute of Mental Health, one of 27 institutes and centers within NIH.

Insel discussed the government role in partnerships by focusing on biobanks, biomarkers, and drug development, pointing out opportunities and challenges in each area. In the area of biobanks, NIH already supports

a large number of often disease-specific, large-cohort studies that collect biosamples. A preliminary estimate of the number of such studies involving more than 5,000 subjects was 139 altogether—90 domestic and 49 international, with some 5 million people involved. These studies are not integrated or standardized, yet the government investment in them could be of great public interest and use.

The collection, storage, and use of biological specimens in biobanks offers the opportunity to look at risk and exposures prospectively as well as retrospectively in a representative sampling of a large population. Biobanks also can be mined in new ways as technology and concepts develop. However, several barriers exist with regard to biobank development, maintenance, and use, including confidentiality concerns when obtaining consents for broad-based studies or sharing of samples, a lack of standardization for collection, handling, and storage, limitations based on the sampled population, and the overall expense.

By examining the NIH's efforts in the area of biobanks and large cohort studies, a number of possible opportunities to improve or leverage the investments that have been made present themselves, said Insel. The samples that are collected could be improved by thinking about how to sample a population that is actually representative of the United States. Standardized approaches in terms of consent, the kinds of information collected, and the handling and distribution of samples, according to Insel, all could lower some of the barriers to the greater use of biobanks. Additionally, the experiences of other countries in establishing and using biobanks offer lessons for the United States as it moves forward.

In the area of biomarkers, four years ago the Foundation for NIH launched the Biomarkers Consortium as a joint effort with the Food and Drug Administration (FDA) and pharmaceutical and biotechnology companies. The consortium, which now has a large number of for-profit and not-for-profit partners, is organized around four steering committees in the areas of neuroscience, cancer, metabolic disorders, and other disease or scientific areas. The goals of the consortium are to develop biomarkers for diagnosis and treatment, and there already have been a number of examples of success. Funding has come largely from industry, with NIH providing samples or other support.

The consortium provides a valuable opportunity to share resources, said Insel, and the involvement of FDA has great advantages, but there have been barriers to progress. One has been a clash of cultures. "The academics are looking for papers, the industry reps are looking for products, and the NIH folks are often arguing about whether there's public health impact," said Insel. There also have been issues about discovery versus the development of biomarkers and about whether industry representatives can speak for their companies. Garry Neil added that "there's been a lot of

good progress made . . . and we need to continue to work together to figure out how to optimize these public–private partnerships . . . but we haven't completely figured out how to get the most out of it."

When asked what he would do differently if he were setting up the collaboration today, Neil highlighted several lessons learned from the experience. More emphasis should be put on the science as opposed to the legal aspects of the venture. The areas and topics to explore should be defined at the beginning of the partnership. Participants should be better prepared for areas where the science is not mature enough for development. A mechanism should be in place to allow funding of individual investigators or labs. The executive committee should be involved early to provide direction to the process. Insel added that the best ideas also need to be identified and brought into the program.

Finally, in the area of drug development, Insel pointed out that NIH is very aware of the problems that exist. The number of new drugs in the pipeline has been dropping, and the biotechnology industry is producing very few new candidate drugs (Figure 4-1). In response, the recent health care reform legislation created the Cures Acceleration Network, which would be a half-billion-dollar effort to create an integrated approach to drug discovery led by NIH. The consortium would look first at neglected diseases and then at more common diseases. "We're not going to replace pharma," said Insel, but "NIH could become a different kind of player. We've got some challenges not only with where we play, but how we play . . . we have to re-engineer the pipeline as well as [think] about how we catalyze discovery in that pipeline." However, using public money for drug development is a

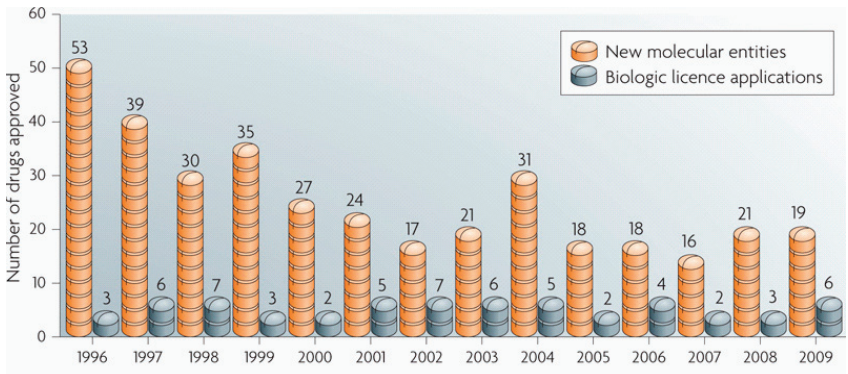

FIGURE 4-1 New molecular entity approvals.
SOURCE: Hughes, *Nature Reviews Drug Discovery*, 2010.

risky venture, according to Insel. NIH does not have great expertise in this area, it is expensive, and intellectual property issues need to be resolved.

Conflict of interest also poses a problem, said Insel. NIH has been thinking about whether there "are issues about how academia and government scientists interact with industry that need to be managed in a different way going forward, because this has been a source of real despair for the last couple of years, both I think on the industry side and on the NIH side." Kelly Edwards, associate professor of bioethics and humanities at the University of Washington School of Medicine added that, in terms of conflicts of interest in partnerships between government and industry, people need to trust the institutions set up to develop new knowledge, which may require an "honest broker" for data interpretation and management. Insel agreed that ensuring public trust is "a really serious problem." NIH has been developing and instituting new regulations governing conflicts of interest, although other issues also have to be resolved. "This needs to involve more than just industry, academia, and NIH and really needs to bring the public into the conversation." When the research enterprise fails to deliver cures, people begin to wonder who is working for the public good as opposed to personal gain, Insel said.

In all three areas of biobanking, biomarkers, and drug development, NIH plans to emphasize standardization, integration, and sharing. Insel also quoted a recent paper on the pharmaceutical industry's grand challenge: "Good process will never substitute for good people or good science" (Paul et al., 2010). "We can spend the whole day talking about partnerships," Insel said, "but unless there's really very compelling science to drive it, we're wasting a lot of time in thinking about this just being a process problem."

ADVANCING TECHNOLOGICAL ACHIEVEMENTS THROUGH COLLABORATION

Christopher Beecher, research professor at the University of Michigan's Center for Translational Pathology, described the formation of a metabolomics consortium devoted to identifying all of the small molecules in a biological sample in order to discover those which are associated with the presence or progression of a disease. The rationale behind developing a consortium around metabolomics is the low compound identification rates in traditional studies. For example, in a recent study, Beecher and his colleagues tracked approximately 1,200 compounds across 262 samples taken from patients with prostate cancer (Sreekumar et al., 2009). The problem is that he and his colleagues were able to identify only about 37 percent of the compounds that they were tracking and there were many unknowns

that were statistically significant. "That's the real bugaboo in many of these [studies]," he said.

Beecher decided to confront the problem of low identification by creating the Human Blood Plasma Metabolome Consortium with the goal of isolating and identifying every compound present at a concentration of more than 0.01 nanomoles in a very large quantity of human plasma. Bristol-Myers Squibb, Pfizer, Takeda Pharmaceuticals, Human Metabolome Technologies in Japan, and Agilent Technologies all agreed to fund the project. "The consortium was created to find a solution in which a number of companies could join together to do something that no particular group could do . . . through any other means," according to Beecher. The collaboration sought to develop reproducible systems, platforms, and protocols to separate and detect these molecules. All of the results are published after a short embargo period.

All members benefit from participating. In the case of the university, they are "the publishers of the blood plasma metabolome." The industry members benefit by the direct knowledge they have gained. "If we are successful—and at this moment we are being tremendously successful—we think that this will be a large plus, ultimately to be released to the public, and [will] be for the benefit of science."

Setting up the consortium, however, took longer than expected—about a year and a half, said Beecher—with universities posing more obstacles than pharmaceutical companies. "The real problem was getting the university to understand and to not put up red flags."

A major concern in forming the consortium was intellectual property. The organizers of the consortium decided that analyzing normal plasma would reduce the intellectual property issues. The legal experts consulted while the consortium was being formed decided that it would be easier if diseased tissues were not analyzed. "This is not a biomarker discovery attempt," said Beecher. "This is purely an attempt to characterize, as fully and completely as we can, what a normal, very diverse human population looks like." Thomas Insel responded that this type of approach would be a serious barrier to progress. "How do you get past that? What are you going to do when you want to study disease?" Beecher replied that the consortium was seeking to produce information that could be used by everyone, just as SEMATECH sought to provide technology that could be used by all of the companies in the semiconductor industry. Stephen Friend observed that "if we as a group were to shy away from working together on disease biology because of IP issues . . . we're in real trouble." Beecher emphasized that universities are risk averse, and to get the consortium funded within an academic environment, it needed to stay away from biomarker development.

OPEN ACCESS PARTNERSHIPS

Partly because of the built-in conservatism of the peer review process, scientific research tends to focus on certain areas and overlook others. For example, 10 years after the human genome was sequenced, 90 percent of the research articles on protein kinases are on just 10 percent of the kinases, even though genetic data indicate that many other kinases have effects that should be investigated. Researchers tend to work in a "tiny universe," said Aled Edwards, professor of medical biophysics at the University of Toronto and director of the Structural Genomics Consortium, "and that's a serious problem."

The Structural Genomics Consortium was established in part to overcome the conservatism of much research. Its goal is to produce 1,000 three-dimensional structures of therapeutically relevant biological targets, along with 100 structures of parasite drug targets. It is funded by the Canadian government, has a board of directors and a scientific committee, and oversees work in laboratories in Toronto, Oxford, and Stockholm. As director of the consortium, Edwards makes many of the managerial decisions. "Don't run projects by committee or consensus," he said. "If you can't find the right person to run it, don't even start."

The consortium made an early decision not to pursue intellectual property, which makes negotiations with partners very easy. "If they don't buy in, we walk away, it takes about two minutes." The consortium generates data quickly and puts it in the public domain without embargoes and well before the publication of papers describing the results.

The consortium has met its major milestone a year in advance of projections. The consortium now contributes more than 30 percent of the annual global output of human protein structures and accounts for 15 percent of the total output. Its scientists also have published papers in a wide variety of high-profile journals.

The keys to success, he said, are to establish clear and quantifiable objectives, create value for all participants (publications for academics, deliverables for industrial participants), and assume the best in collaborators. "Sometimes if you're open, you are going to lose and get burned, but 95 out of 100 times, it's going to work. Just let go of the 5 percent and move on."

The consortium now has moved the precompetitive boundary by beginning to work on probes for nuclear protein receptors. Whenever reagents and other tools are available to work on a particular receptor, the number of publications on that receptor leaps upward. Yet many interesting genetic targets have received very little attention. As a result, the consortium has organized an effort to make chemical probes available for cell-based assays. The best medicinal chemists are in industry, and the corresponding biolo-

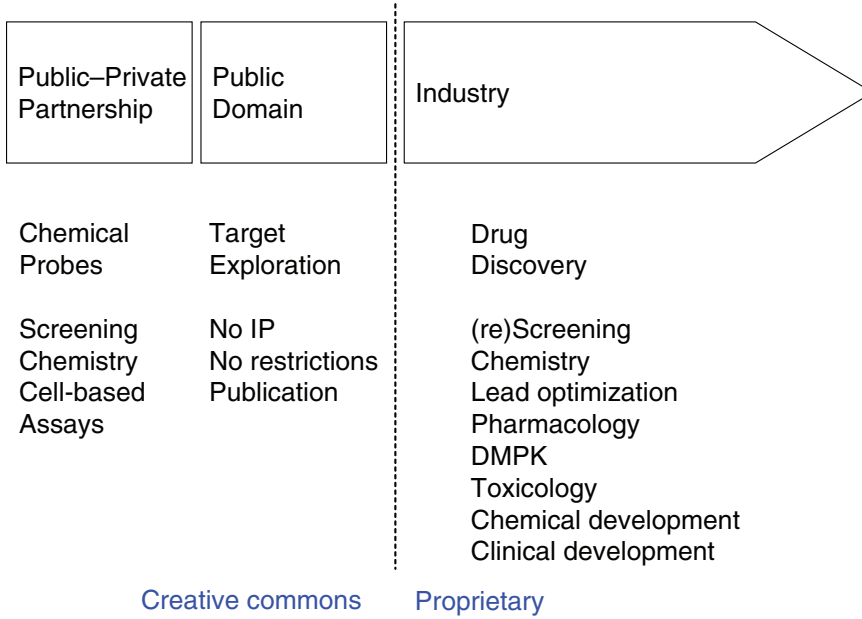

FIGURE 4-2 Model for precompetitive chemistry.
NOTE: DMPK = drug metabolism and pharmacokinetics; IP = intellectual property.
SOURCE: A. Edwards, IOM workshop presentation, July 22, 2010.

gists are in academia, so the consortium created a public–private partnership to produce high-quality tools that can be used for drug discovery and other applications in the proprietary domain (Figure 4-2). Both academic labs and companies are joining the partnership, and tools are starting to be released for use. Edwards cited as an example a G9a methyltransferase probe. Data generated with the probe are freely available on the consortium's website. The idea, said Edwards, is "to seed this field with papers, and then hopefully more and more people will get at it."

The final precompetitive barrier Edwards discussed is the failure of novel drug targets in clinical proof-of-concept trials. Data from these failures tend not to be released, which means that patients receive ineffective or even harmful drugs. Edwards suggested that these trials should become precompetitive research. "We should form a precompetitive consortium whose mission is to do open access [research], all the way from inventing the molecule to the phase II [trials]. . . . All the patients will be involved and know what's going on, and we'll make all those data available." As soon as targets are validated, companies can then use that information to make medicines.

ACCESS TO LARGE-SCALE DATA NETWORKS

Technologies are being developed today that will allow many thousands of patients to have their genomes sequenced. Interactions among vast networks of proteins and metabolites will be mapped. The function of noncoding RNA molecules will be explored and related to the functions of other molecules in the cell. The functions of biological molecules will increasingly be connected to influences in the environment. Yet even these slices of biological function, by themselves, will not be sufficient to understand the mechanisms of disease, said Stephen Friend of Sage Bionetworks. All of this information and more will have to be combined into what he called "more causal or predictable models" of disease (Figure 4-3).

This work will take decades, but already this approach has begun to pay off, said Friend. Genetic association studies have been combined with genome-scale profiling to provide unbiased views of molecular physiology as it relates to disease phenotypes. Pharmaceutical companies are using this approach throughout the drug discovery process. Academics are writing papers on complex networks that have far-flung applications in research and in industry.

Public–private partnerships will be essential to host the data and

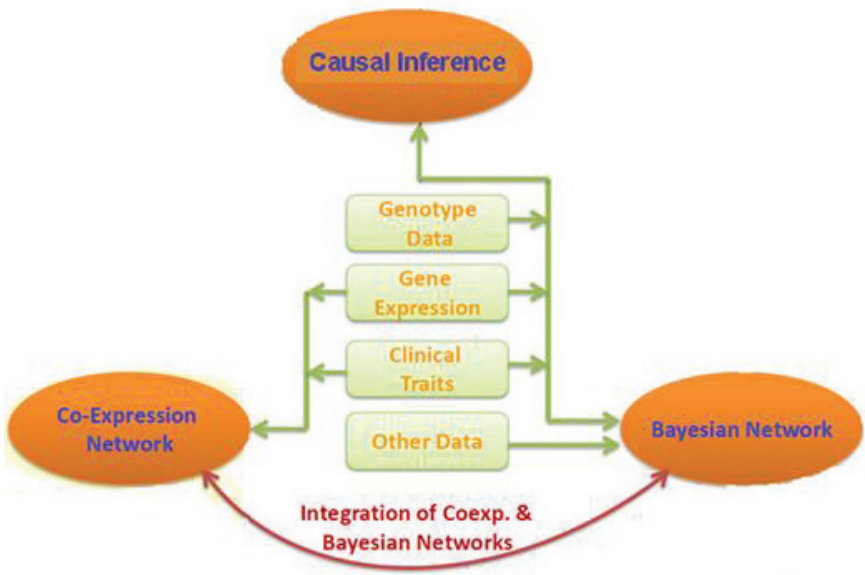

FIGURE 4-3 Integration of genotypic, gene expression, and trait data.
SOURCE: Adapted from Friend, IOM workshop presentation, July 22, 2010.

develop evolving representations of disease, and these partnerships will require significant resources over long time periods. The way to secure this kind of support, said Friend, is to view disease biology as precompetitive research. "We can't take this on as a single company or single institute."

That idea is the motivating concept behind Sage Bionetworks, which is based at the Fred Hutchinson Cancer Research Center in Seattle. The organization functions as a commons that produces long-term gains for the entire biomedical community by evolving models of disease. Sage Bionetworks has been pursuing a public-private partnership approach for Alzheimer's disease and has also been investigating nonresponders to cancer treatments through data on gene expression, proteomics, metabolomics, and other molecular data. Sage Bionetworks is "curating new data sets that should be [available] and . . . putting up tools that allow people to work together to build probabilistic causal models of disease."

In traditional research, an investigator who gets a grant thinks that he or she can keep the data generated by that grant until postdocs have gotten everything they can out of the data. "That prevents data flow from occurring," said Friend. Physicists have learned to live in a world where microattribution and citation do not rest on publication. He noted that young scientists are already more comfortable living in a more collective world. "In 10 to 20 years, the careers of people will be based on who knows who did what with whom," said Friend.

Sharing of data and the development of common standards need to occur at a technical level, but they also need to occur at a cultural level, stressed Friend. "Think of a world where interlab communication is equal to intralab communication," said Friend. "Think of a world where the ability to talk back and forth between labs is the same as it is within labs. To do that, we've got to have funders be able to agree that their investigators will be sharing data in certain ways."

Pilot projects can demonstrate for investigators how to share data. For example, making the data on controls for all clinical trials publicly available could be a model for making data accessible. Another possibility would be to define intellectual property (IP)-free zones, said Friend. "Why don't we define certain diseases, where everyone who's working in that disease says, 'I'm not filing IP'?" New models and fundamental changes in how science is funded and rewarded are necessary to head toward a world in which contributors are more distributed, urged Friend. The patients and their disease foundations will be at the center of this world surrounded by companies, researchers, and government agencies.

5

The Use of Biospecimens in Precompetitive Collaborations

Key Points Raised by Speakers

- Viewing biobanks as national or international resources requires strict adherence to high standards of quality, confidentiality, and fairness.
- Ensuring that consent provisions are observed requires centralized control of biobanks and associated databases.
- High-quality data can be derived only from high-quality biospecimens.
- Strong incentives are essential for companies to invest in biobanks that are used for collaborative efforts.

Biospecimens stored by investigators in industry and academia and the data derived from those biospecimens represent a considerable resource of genetic and genomic information that can be used to develop individualized treatment regimens or even drug and diagnostic devices. Since the value in these samples lies in their inherent potential for use in discovery, biospecimens are prime candidates for collaboration and coordination. However, in order to achieve this promise, their quality must be high, related data annotated, and their accessibility assured since the majority of collections are fragmented and isolated. With this in mind, the workshop participants were asked to address the following points in regard to potentially sharing biospecimens in a precompetitive collaboration:

- What are the unique issues in sharing biospecimens?
- What have speakers learned from their initiatives that could be used to find the best practices for biospecimen and data sharing?
- What incentives should or need to be in place to encourage sharing of specimens and data?
- What key structures or rules are required to establish a framework for sharing biospecimens and data?

STANDARDS FOR BIOSPECIMEN QUALITY

The quality of the data derived from biospecimens can never be higher than the quality of the analytes from which the data are derived, said Carolyn Compton, director of the Office of Biorepositories and Biospecimen Research at the National Cancer Institute (NCI). However, the quality of human biospecimens is often either unknown or low, which can harm research that uses these samples. The question she posed was not "can I get access to existing samples?" but "do I want them?" "The roadblock to success and to greater efficiency in the translational research realm is related to the lack of high-quality human samples," said Compton.

The NCI and other government agencies are making major investments of public dollars in research projects that depend on high-quality human samples. The NCI alone invests $50 million to $70 million annually in biobanking efforts of various kinds, but many researchers do not understand what needs to be done to achieve high quality. An evaluation of the biobanking system found different collection, processing, and storage procedures; differing degrees and types of annotation; variations in the scope of patient consent; differing material transfer agreements; inconsistent information technology support; and inadequate access policies. Most researchers also have few incentives to share their samples, further contributing to wide variation in the quality and accessibility of samples for research.

In acquiring biospecimens for the Cancer Genome Atlas Project, which is seeking to identify genomic changes occurring in cancer and make those data publicly available, NCI identified a large number of problems with existing samples. The quality of existing samples in biobanks is typically overestimated, said Compton. The collection of normal control samples is not routine, and clinical data on specimen donors are not readily available. Even if a specimen looks pristine under a microscope, according to Compton, its molecular quality may be low. The NCI was seeking to collect 1,500 high-quality samples for the pilot of the Cancer Genome Atlas Project, yet in 3 years it was unable to do so, said Compton.

Biospecimens are subjected to "industrial-strength biologic stresses" once they are collected, said Compton. Even the extent and type of molecular changes induced in acquiring a sample for research are largely unknown.

Variables before acquisition include exposure to antibiotics or other drugs, the type and duration of anesthesia used during surgery, and the arterial clamp time. Variables after acquisition include the time at room temperature, the temperature of the room, the type of fixative used, the time spent in the fixative, the rate of freezing, and the size of aliquots. Any of these can have dramatic effects on a biospecimen (Figure 5-1).

As an example, Compton cited a study of colon cancers showing that the time of intrasurgical ischemia while a tumor is anoxic dramatically affects gene expression in removed tissues (Spruessel et al., 2004). Even standard biomarkers for colon cancer alter their expression depending on the amount of time a tumor spends sitting at room temperature after removal. "If you let this specimen sit around for a half an hour before you fix or freeze it and then do your tests, you will be led to think that artifactual upregulation of this protein or gene actually represents the disease," related Compton. This will require surgeons to change some of their practices. "For surgeons, it's a cultural issue of their not feeling a sense of professional responsibility toward the sample. In other words, when they remove the tumor, all of their focus goes back on the patient on the table, and the tumor itself, the reception specimen, falls into no-man's land where custodianship is concerned. It has not yet become the pathologist's professional responsibility, and the surgeon does not regard it as his or her

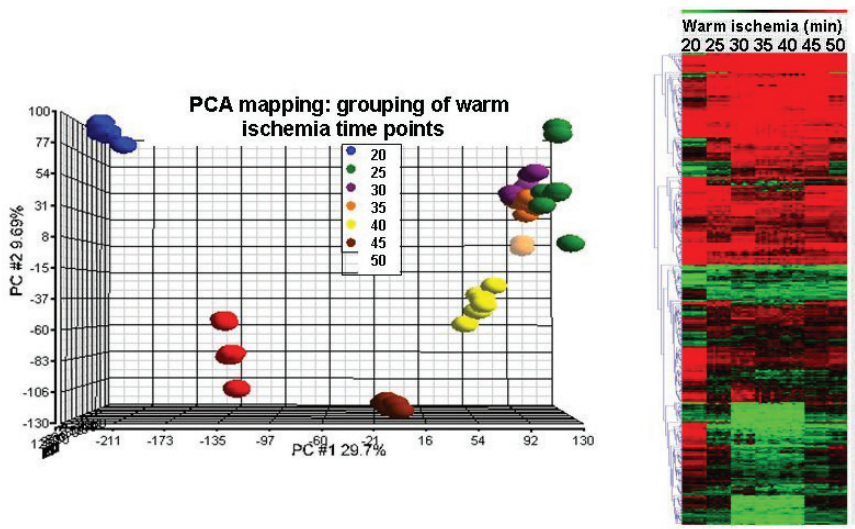

FIGURE 5-1 Changes in gene expression over time after intrasurgical ischemia. SOURCE: Compton, NCI Indivumed Study, 2010.

professional responsibility." Either new ways need to be found to control the influences on a biospecimen or it should not be assayed, Compton said, "because it will give you the wrong answer."

Liquid specimens such as blood plasma are subject to even more variables. According to Compton, "with the stakes going up with proteomics, genomics, metabolomics, and other 'omics' experiments, you stand a great risk of misinterpreting artifacts as a biomarker unless you know what happened to your specimen before it went into your analysis."

To counter these problems, the NCI has been taking a stepwise approach. It began by developing best practices for biospecimen resources (NCI, 2007) that provide a baseline on which to build as the science evolves. These best practices represent a set of unifying policies and procedures for biospecimen resources across the United States, although NCI does not have the authority to enforce these guidelines, which means that they must be adopted voluntarily. However, Compton did suggest that a new focus on the quality of samples will create incentives for scientists and publishers to question the quality of the samples on which research or a publication was based, and "this will change the culture." Also, the existence of a guidebook and an expanding science base on the factors that affect samples will lead researchers to want to do the right thing. Finally, NIH could decide that best practices should be more than voluntary and make adherence to standards a condition of receiving a research award. "We require our scientists to report on the care and feeding of the animals but not the care and feeding of the human specimens that they use in our funded research," said Compton.

The guidelines include recommendations for technical, operational, and safety practices; quality assurance, control, and management; implementation of enabling informatics systems; ethical, legal, and policy issues; reporting mechanisms; and administrative and management structures. "A biobank is no longer regarded as the minus 80 degree freezer in your hallway with an Excel spreadsheet Scotch-taped to the door," said Compton.

Recognizing that the science of biobanking is weak, the NCI also has set out to strengthen the evidence base for biobanking. It is building a national disease biobank called the Cancer Human Biobank (caHUB) in which all the variables currently known to be important are being investigated. Launched with funds from the American Recovery and Reinvestment Act of 2009, it is initially a government-owned and government-operated enterprise, but the vision is that ultimately it will be a public–private partnership. "It will be a unique, centralized, not-for-profit public resource that will be a source of adequate and continuous supply of human biospecimens and associated data of measurable high quality within an ethical framework, and a source of high-quality biobanking services for the community," said Compton.

All the data associated with the biobank will be in the public domain, according to Compton. Tumor samples and data will be collected from hospitals approved by the Commission on Cancer, which will ensure that patients receive a certain standard of care and that standardized data elements are collected on every cancer patient. The biobank will be centrally managed and quality controlled but will provide access to all members of the community.

Compton expressed the firm belief that the biobank should be in the precompetitive space. "No one can do this alone, and everyone will benefit from it." In particular, drug development relies in crucial ways on the quality of biospecimens, and the decision to move forward based on results from biospecimens of unknown quality is one reason why drug development is so expensive and so often fails. "This is going to require a seismic shift in the way we think," said Compton. "If we think it's too expensive, or too labor-intensive, or too time-consuming to do it right [the first time], I don't know when we'll have the time or money to do it over and so I would suggest that this is a just-in-time step to invest in the right stuff that is going to move the agenda forward, and it's a perfect space for a public–private partnership."

LINKING HEALTH OUTCOMES DATA TO BIOREPOSITORY SAMPLES

There are many potential obstacles to the access and utilization of biospecimens, said Cynthia Helphingstine, president and CEO of the Fairbanks Institute for Healthy Communities. Biospecimens may not be available, or their quality may be highly variable. Phenotypic data may be incomplete, or access to the biospecimens or associated data may be restricted. Longitudinal outcomes data associated with the biospecimens may not be available. Biospecimens may not have adequate consent, or biospecimens from appropriate controls may not be available.

Overcoming these barriers was the motivation behind the creation of the nonprofit Fairbanks Institute for Healthy Communities in Indianapolis in 2006, noted Helphingstine, with seed funding of $10.5 million from the Richard M. Fairbanks and Guidant Foundations in collaboration with BioCrossroads, which is the State of Indiana's life sciences initiative; the Indiana University School of Medicine; the Regenstrief Institute, Inc.; and other community partners from central Indiana.

The vision of the institute, according to Helphingstine, is to conduct a longitudinal study of Indiana's population in which biological specimens are linked with clinical outcomes data from the Indiana Network for Patient Care to create a novel and powerful research platform that will facilitate basic and translational research breakthroughs and lead to

improved patient outcomes. Also, by engaging the community as a partner in the creation of the institute's research platform, resultant medical breakthroughs would have the potential to create civic pride among the citizens of Indiana and facilitate community participation in all Indiana research studies, said Helphingstine.

As is the case elsewhere, Indiana has high rates of smoking, obesity, cancer, and heart disease. "Finding health-challenged populations to study would be, unfortunately, relatively easy in Indiana," said Helphingstine. The state also has the Indiana Network for Patient Care, which is a regional health information exchange that serves as a repository of clinical data for health systems in central Indiana and represents about 1.6 million patients. The network was founded by the Regenstrief Institute more than a decade ago with the idea of providing clinicians with the information they need whenever they need it. The network also has access to health information going back about four decades to some of the nation's first electronic medical records. "You can go back and pull out someone's blood glucose or glycated hemoglobin from 1978, and it's there. Not on everybody, but it does go back a long way . . . and importantly, these health systems are continuing to generate information."

This ability to link data and perform retrospective and prospective analyses on large numbers of patients contributed to the vision of creating a resource for the genomics, proteomics, and metabolic studies that are needed today. With the ability to query more than 8,000 clinical, laboratory, and outcome variables, "you can design studies that never were possible to think about before." As an example, Helphingstine mentioned a study enabled by the institute on coronary artery disease, which is examining 1,500 individuals—750 individuals with documented history of the disease and 750 in the control group, with the control population being annotated to ensure they are not on statins, do not have diabetes or hypertension, and so on. Clinical information on study participants can be retrospectively and prospectively updated from the electronic medical record at any time to gather additional phenotypic information on study participants and to select biospecimens for discovery and validation studies.

The institute has 16 sites at which patients are enrolled and consents obtained. Partner organizations provide storage and analysis services. The Regenstrief Institute links the information with the biological samples, which are available to academic, government, and commercial researchers from all around the world.

The institute has made a major effort to engage with communities through roundtables, partnerships with community organizations, and community events (Figure 5-2). Consent is a major issue with the institute's work, and "we make sure the people in our study understand that these samples will be used by academics, government, and commercial research-

FIGURE 5-2 Community engagement strategy.
NOTE: CHEP = Community Health Engagement Program; CTSI = Indiana Clinical and Translational Sciences Institute.
SOURCE: Fairbanks Institute for Healthy Communities, 2010.

ers." People in the study are told that their medical record data will be made available and they may be contacted for more samples or information in the future. They also are informed that information may be obtained from prescription and payer databases.

Although medical record data are disclosed, people are informed in the consent process that they will not receive any information about themselves, said Helphingstine in response to a participant question. However, she continued, if an investigator found something he or she felt was imperative to be reported back to a participant, the Institutional Review Board could make a determination on contact and, if appropriate, the Regenstrief Institute can reconnect the data to the person's name.

In terms of IP, the institute does not pursue any, said Helphingstine. "It is not our job to own the IP. We just provide the samples, we hope industry does something with it, we hope academics do things with it."

Moving forward, Helphingstine related, the Fairbanks Institute would like to initiate new longitudinal studies as collaborative efforts. "We really would like to do things with collaborators where people will really want to put data back into our database, so that [information] would then be available for everyone that wants to use our samples."

SUSTAINING ACCESS TO BIOSPECIMENS

The UK DNA Banking Network (UDBN) is an "infrastructural research project," said Martin Yuille, a reader in biobanking and co-director of the Centre for Integrated Genomic Medical Research at the University of Manchester. It is both an infrastructure and a research project designed to ensure access to annotated samples and data including genomic, genetic, and phenotypic information. The UDBN does DNA extraction and quality control; maintains cell lines; stores, retrieves, distributes, and tracks samples and data; and maintains an identifying link to all annotations. It holds all data centrally to achieve the goals and standards of the UDBN, which also allows for consent provisions to be attached to a sample and its associated data so that samples and data can be withdrawn from the biobank if requested. It currently manages about 60,000 samples and has distributed 80,000 aliquots. Assurance from the International Standards Organization ensures consistency, imposes continuous quality improvement, and reduces problems associated with staff turnover and succession.

In the UDBN's first phase, it established a biobank for advanced sample management by collating samples from disparate collections, standardizing them and their associated data, and making the samples available for further investigation. In phase 2, it is undertaking advanced management of the sample annotations, including phenotypic data from electronic health records and other sources (Figure 5-3). Any researcher will be able to browse the resources and request access to the data and the associated samples. The samples and data are treated as "national resources" that must be readily available to those deemed to be bona fide collaborators, whether they are from commercial companies, universities, or some other organization.

This arrangement has generated some new issues that have not been dealt with before, said Yuille. The idea of biospecimens as a "national resource" is a shift comparable to that of the transition from hunting and gathering to agriculture. The development of such a resource requires very broad consent. It also requires a chain of quality at all steps, "from the patient to the paper," said Yuille. Additionally, a system needs to be implemented to guarantee return of data back to the repository from those that have been granted access to specimens. The movement of samples and data across borders requires a global vision for sharing. "Biobankers in the [United] States need to be talking to biobankers in Europe and in the Far East and everywhere else in the world," continued Yuille, "about how we're going to improve the movement of samples and data."

Finally, there needs to be respect for all of the stakeholders involved in this work, added Yuille. The UDBN has adopted a "fair access" charter that spells out how various stakeholders should be treated (Yuille et al., 2010).

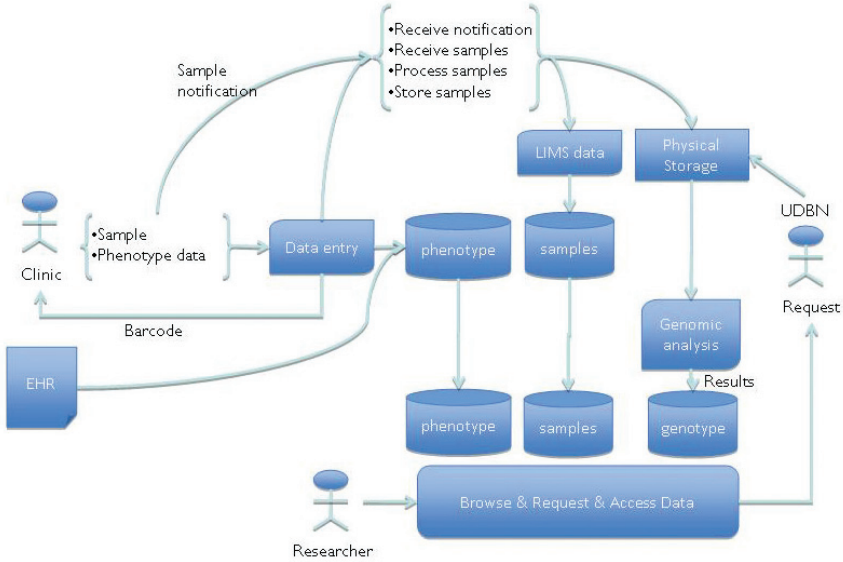

FIGURE 5-3 UK DNA Banking Network advanced management of annotation.
SOURCE: UK DNA Banking Network, 2010.

Fairness to the subject involves guaranteeing privacy and confidentiality, the ethical use of samples and data, consent management (including national and open methods to permit effective withdrawal of consent), and public engagement with the work and its goals. Yuille pointed out, however, that "The UK Biobank model is that you have donated your sample to UK Biobank and that's the end of the matter. . . . We will not tell you anything about the genetic outcomes, for example, of an analysis. We will tell you if your blood pressure is too high when we see you, on the day that we see you, or we'll tell your GP, but beyond that we won't go."

Fairness to the collection entails giving the people who made the collection the right of first access to the samples. In this way, said Yuille, they can carry out the research for which they received funding to create the biospecimen collection.

Fairness to the recipient of the samples, according to Yuille, requires collaborative management to ensure transparency of a sample's use, access to published and unpublished data about the sample, long-term availability of the sample, and a minimum of administration. "We don't want recipients having to spend forever filling in forms in order to get access to samples or data."

Finally, fairness to the collectors' and investigators' institutions requires long-term tracking and management of samples.

The sharing of samples and data is not a major technical problem, concluded Yuille. It is more of a cultural problem. Extensive national and international discussions and collaborations have been and will continue to be essential to win an understanding that competition should be between ideas, not about de facto control of biological samples.

CREATING A NATIONAL VIRTUAL BIOSPECIMEN BANK

The goal of the Clinical Translational and Science Awards (CTSA) Biobank Consortium is to develop a virtual biobank using an automated online sample request management system for use across multiple CTSA centers with samples maintained at their home institutions, said Lorraine Frazier, professor of nursing and assistant dean and department chair of Nursing Systems at the University of Texas Health Science Center in Houston. At the Houston site, the biobank began as a manual system with more than 48,000 patients and more than 188,000 samples. About 70 percent of the biobank was collected with standardized protocols, and more than 12,000 samples have been distributed to 46 researchers since 2002. "We're not about giving millions and millions of samples away," said Frazier. "We're about being effective and making sure samples are used effectively."

The consortium has created and tested a prototype custom biobank software application and associated technologies. It also piloted the electronic capture of patient consent variables. A requirement for joining the biobank is the automation of an investigator's samples. Currently, the University of Texas Health Science Center at Houston has partnerships with the University of Michigan, the University of Texas Health Science Center at San Antonio, the University of California at Davis, Indiana University-Purdue University Indianapolis, and the Baylor College of Medicine. "We're all coming together to collaborate and connect with an automated system where we can ask for samples and disburse those samples."

The Biobank Executive Steering Committee agrees on policies and procedures for the biobank. These policies and procedures are agreed to and used by all sites and by the Web application when requesting and managing samples. The Web application searches all the individual sites and coordinates request procedures, notifications, and NIH reporting requirements. Samples are then delivered to the researcher from the sample owners at the local sites.

"The samples belong to the PIs [principal investigators], they don't belong to us," said Frazier. "PIs don't like to let go of their samples. They talk about sharing them, they love to talk about collaborating, but when it gets right down to it, they have to have . . . say over the samples." PIs thus have the ability to decide whether or not to collaborate on a research project.

Stephen Eck from Eli Lilly and Company pointed out that the federal government paid for the collection of samples and that giving PIs complete control over how they are used is unlikely to be in the public's interest. Frazier agreed but observed that "most of the PIs across this nation feel that they own those samples. A big cultural shift needs to occur. We're asking a lot. I think we're making progress, but I agree it could hinder innovation and investigation." Kelly Edwards added that ownership is not just about control, it is also about responsibility. PIs often feel a stewardship obligation toward the participants they have recruited into their studies. The participants trust the fact that the PI is going to make decisions about data release, data use, and so on. This trust will have to be maintained in moving toward a more federated model, she said.

Cost and time are some of the issues that have prompted PIs to refuse to share their samples, according to Frazier. In response, the consortium is developing a business model that would entail charging for the samples. "We don't make money, but we'll have enough money to pay those individuals to actually pull those samples and get some of that work done." Martin Yuille pointed out that his group has been required by the Medical Research Council to implement a cost recovery policy as well, but the strategy "doesn't really work." Sample requests and the subsequent payments are irregular, but employees need to be paid on a regular basis. As a result, his organization has to take on other projects and charge for those projects to pay the people who are manning the robots in the UDBN, and even that does not cover all the personnel costs. "The cost recovery element isn't that great," he said.

Participating sites are expected to provide oversight of the biobank team personnel and to sample holders who contribute at their sites, said Frazier, participate on the executive steering committee and provide funding for personnel and technical resources. Individual sites also make sure that sample-related data, clinical data, and patient consent variables are migrated from paper to electronic format; that samples and data are consented for secondary use; and that the data are validated.

The benefits of membership include improved synergy and interactions across the institutions through sample sharing, acceptance of a business plan and cost recovery model, use of the online sample request management system, and lower costs for entry and maintenance than for the closed data models inherent in commercial software solutions.

Cultural considerations are important, said Frazier. "We're shifting from competing to collaborating. We've made great strides, but we have a long way to go."

CLINICAL AND GENETIC DATA ACCESS IN THE PHARMACEUTICAL INDUSTRY

Pfizer studies 30,000 to 40,000 people in randomized clinical studies every year, which represents a rich source of information for research collaborations, said Sally John, head of Human Genetics at Pfizer. Since 1996, Pfizer has been recruiting people in its clinical trials to contribute to a biobank of genomic, biofluid, and tissue samples. However, informed consent for the trials allows for only the assessments described in the protocol, requiring a different approach to use specimens for other purposes. Thus, participants are asked for additional consent to participate in genomic, proteomic, metabolomic, biomarker, and other studies. John said that 70 to 80 percent of clinical trial participants give samples when asked if they want to participate. These samples are of use within Pfizer, but they also have many potential uses outside the company; thus far, only 35 percent of the samples have been used in research projects, leaving an intact, substantial biological resource, said John.

Industry has many incentives for investing in such biobanking efforts, according to John. Such investments demonstrate a commitment to improving science in both academia and industry with a particular focus on human research. They contribute to the development of robust predictive models of disease. They enable meta-analyses of multiple data sets, which provide more power to detect and estimate modest effect sizes and conduct rapid replication and validation of exploratory findings. They also attract funding for clinical research to address questions that are common across the industry.

John cited two examples of collaborative studies, one that benefited from industry inclusion and one that could have. A paper published in *Nature Genetics* used almost all of the academic samples that were available at the time to investigate a genetic variant involved in drug-induced liver injury due to flucloxacillin (Daly et al., 2009). The research brought together several academic partners and was funded by pharmaceutical companies and the Wellcome Trust. "The beauty of this paper is it was overwhelmingly robust and validated the result in its first publication. We didn't have to wait for another publication to come out and validate it," said John. The second paper used large-scale association analysis to identify twelve type 2 diabetes susceptibility loci (Voight et al., 2010). The sample size in this study was 45,000, but according to John, "we could have doubled the power of this study by making [industry] samples available for this type of research."

Participation in large-scale studies is also beneficial for junior faculty. They "provide opportunities for young researchers to ask questions that were simply not addressable prior to having all of this data together

in the same place. I think we will see, over the years, that this type of multicollaborative research actually provides more opportunities for young researchers to flourish," said John.

Several factors can inhibit the use of Pfizer's samples, though, continued John. The consents allow access to data only through a collaboration with Pfizer. However, the business value of the collaboration is considered low internally, partly because there is a view that large consortia never deliver anything. Additionally, external and internal stakeholders may need to okay or endorse a specific project, and academic partners sometimes expect that industry will foot the bill for the research.

Pfizer is trying to think internally about how to implement some best practices related to its collection of biospecimens. The company is looking to simplify the process to access its biospecimens and data and is contemplating seeking endorsements from stakeholders early. One approach would be to standardize the conditions of access across studies, which is something that John said should be done across the entire industry. As an example, John said she personally would not have a problem with putting all of the data associated with the controls for a study in a publicly accessible database, though that may "not necessarily represent the views of Pfizer. I think, in terms of standardizing and simplifying the process, . . . we don't see any reason why we shouldn't make all baseline data available for comparative arms."

Additionally, all data generated from the studies must come back to a central database for additional meta-analysis so that knowledge and information are continuously built. Industry partners also need to ensure that skilled experts are fully engaged with precompetitive efforts. "You won't get much out of it if you dial into a telecom every six months and stand on the sidelines," said John.

A variety of incentives can motivate companies and individuals to participate in this work. Academic and industry partners both need rewards for making data available. All work coming from the collaboration has to be published. Funding to support the operational aspects of precompetitive research also can encourage participation. "It's not a trivial task to order 20,000 DNA samples for a collaborative research project, and so ways or mechanisms to make it easier for pharmaceutical industries to do that would be welcome." What is needed, said John, is "a commitment in these large consortia to enable all of the parties to access and use the data effectively."

6

Ethical Challenges in the Use of Biospecimens

Key Points Raised by Speakers

- The use of biospecimens and data derived from biospecimens for research entails significant ethical obligations to the individuals from whom those specimens were obtained.
- The scope of consent needs to be clarified to ensure continued trust in the individuals and institutions associated with biobanks.
- Investigators and biobanks need to decide explicitly on the level of identifiability that they will maintain in the specimens and data they use.

Many patients are comfortable with the sharing of their personal biomedical data because they trust the institution asking them to participate, observed Ellen Wright Clayton, professor of genetics and health policy and director of the Center for Biomedical Ethics and Society at Vanderbilt University. When more than 4,000 Vanderbilt faculty and staff were asked whether sending deidentified genetic information to a national database would affect their willingness to participate in a biobank, 69 percent said it would not affect their willingness to participate, 12 percent said they would be less willing, and 18 percent said that they would be more willing. "In general, they don't mind, they think it's a pretty good idea," said Clayton.

Nevertheless, there are serious ethical considerations associated with

the use of biospecimens or data from individuals, according to Clayton. Many of these considerations are related to the idea of informed consent, which rests on the concept of autonomy—that patients should be allowed to decide what to do. However, other issues are also at stake, including control, respect, and expectations. Some research participants, said Clayton, believe that they should not only have control over the uses of their samples and data but also have some stake in the intellectual property that emerges from that use. Questions also surround whether research participants should receive information back from researchers about their samples and whether they should be contacted in the future to give additional samples or information.

Given the wide array of issues, it is important to clarify what is at risk. A tremendous amount of epidemiological research and other types of investigations have been done in the United States for decades without any informed consent or notification whatsoever, according to Clayton. She said that the research community has moved to the point of recognizing that people and communities need to know more about what is being done in the research environment and with their information. This is "an evolution in our ethical thinking that's tremendously important." In situations where people are going to receive information about their samples or be recontacted to serve in future studies, said Clayton, consent needs to be more robust. "You have to look at what's actually at stake," she added. "You can't say 'autonomy' and end the discussion."

As more samples and data are shared, the scope of consent needs to be addressed. Broad consent can never be truly informed, said Clayton. As a consequence, issues of governance become central. The organizations that collect and use research data, according to Clayton, need to decide what they are going to tell research participants; they also need "to realize that informed consent cannot bear the whole weight in this area." People generally want to know what kinds of research will be conducted with their samples and who will be doing the research. For example, research participants are generally more comfortable with academic institutions than they are with commercial entities. "We can agree that this may be misguided, but it's something that we have to consider going forward."

Identifiability is another key issue in the use of biospecimens and biological data. Samples are more useful scientifically when there is more information linked to them. Additionally, linkages create the opportunity to return research results to individuals. However, as more data are linked, the risks to privacy become greater.

An important step, said Clayton, is to eliminate the word "anonymous" from discussions of biomedical research. "All [you] can talk about is more or less identifiable," she said, and as data become more identifiable because of more extensive and robust databases, the important question will be

whether it is appropriate to use them for identification. For example, will the federal government be able to access databases within the government, in academia, or in companies, and if so what will the government be able to do with that information? The question, according to Clayton, "is not whether something is identifiable or not, but who gets access to it and for what purpose?"

Tools are being developed to assess the risks of identification, but investigators and biobanks also will have to decide explicitly about the level of identifiability they will maintain in the specimens and data they use, stated Clayton. Should the collector of data be able to link data or a specimen with an individual? Should a repository? How can good privacy practices be maintained in all institutions? Data use agreements may often be necessary, said Clayton, especially when sharing identifiable data and samples.

The bottom line, said Clayton, is "that the use of data and biospecimens for research entails significant ethical obligations to the individuals from whom they were obtained." Researchers and institutions have to consider carefully what they are asking of participants. They need to figure out how to address participants' concerns. Said Clayton, "we have to think about what we're going to do to protect privacy and identity, and we have to do this going forward in an environment [in which] sharing data and sharing samples are absolutely essential to getting to the kinds of advances in science to promote [the] health care that we need."

DISCUSSION

In response to a question about increasing the diversity of the population represented in biorepositories and how to address the fears of non-white participants about the potential misuse of biological samples, Clayton said that "some of their distrust is well earned." Overcoming these fears will mean earning their trust. "It is community engagement, it is responsiveness, it is including individuals, and [it is] sharing with them why it makes a difference to be involved in this kind of research and doing so in ways that are sufficiently transparent to gain their trust." A necessary step for including African-American, Hispanic, and other non-white populations is to figure out what their concerns are and to address them with transparent policies that hold the system accountable.

Carolyn Compton observed that some patients seem willing to voluntarily give up privacy by placing their information in public places in order to benefit a disease area. Clayton noted that a cultural change is needed to make it safer to put this type of information out there because otherwise patients may take it back. "We should seek to create a society where [such contributors] will not be penalized. [That is an area] where we, as a society, have a capacity to do better," said Clayton.

7

Toward Developing a Cultural, Legal, and Behavioral Framework for Precompetitive Collaboration

Key Points Raised by Speakers

- Diminishing returns in drug development are creating powerful forces for change.
- Establishing IP-free zones would open new areas of R&D to precompetitive collaboration.
- Leadership from both NIH and the pharmaceutical industry will be essential to drive needed institutional and cultural changes.

"Precompetitive collaboration is not a new concept," said Stephen Eck of Eli Lilly and Company. "It's happening, and it delivers results. So the real question is how can we make that happen on a larger scale?"

FACING THE PROBLEMS

William Spencer urged a continuing focus on the basic problem: the number of drugs coming out of the pharmaceutical industry is declining while research costs are going up. It is taking too long to develop drugs and R&D costs are not covering new drug delivery. According to Garry Neil, the high costs of drug development—between $1.2 billion and $1.8 billion per drug—are being driven by biological complexity and by the high rate of failure during development. Only one out of ten drugs pays back its development costs, he said. Viewed in that light, some of the issues discussed

at the workshop are of less importance, Spencer said. "When the surgeon walks in the room and says 'It's malignant,' you don't give a damn about privacy at that point. [The patient only cares about] how are you going to solve that problem for me?"

Spencer said that a leader from the pharmaceutical industry needs to stand up and say, "We've got an issue." The NIH needs to play a role similar to that played by the Department of Defense with SEMATECH, he continued. The industry needs to convince the federal government that it will get products into the market faster and with less expense through a cooperative effort between government and industry. With universities, the desire to protect IP was solved in the SEMATECH case by sending them money. The important issue is to move from basic discoveries to something that will help patients, said Spencer, and "patents in that process are not very important."

Neil cited as major problems an inadequate clinical research infrastructure and antiquated regulatory science. Attention needs to be devoted to creating the right infrastructure to move faster on the clinical side. Additionally, there needs to be a refocusing of research efforts in human systems as "animal models are very imperfect examples of human biology, let alone human disease."

Sharon Terry, president and CEO of Genetic Alliance, expressed the opinion that a crisis is needed to drive the necessary changes, because change is difficult. The current crisis is that "the public understands that we've spent a lot of money on research, and although it's a tiny amount of money when we look at other industries . . . we don't see a lot of results. We might have hyped things in earlier years without meaning or wanting to, and this stuff takes a long time." In order to move forward and develop products, the shared understanding of where and what people can make money on needs to change, she said, which is hard for companies, for academia, and even for not-for-profit foundations such as the one she heads.

A lot of issues facing the field today are transactional in nature, said Geoff Ginsburg. When potential collaborative agreements enter into the legal department, the process slows noticeably. There is a disconnect which needs to be addressed where IP protections can be overvalued while the value of the collaboration itself may be overlooked. Ginsburg supported the idea that studies of disease biology and biospecimens should be IP-free. "There's nothing in a biospecimen that is worth patenting. It's what you do with them," he said. "If we could lay down ground rules and say getting specimens and data out into collaboration or to the public domain is not an IP event, to me that changes the dynamics of the transaction." Terry also called attention to the cultural dimensions of change, which means putting new incentives in place.

DRAWING THE LINE BETWEEN PRECOMPETITIVE AND COMPETITIVE EFFORTS

In drawing the line between precompetitive and competitive R&D, Eck pointed out that one possibility is for everything to be precompetitive before the point of a clinical proof of concept. Another possibility is that even establishing the proof of concept could be a precompetitive and collaborative activity. Several speakers spoke in favor of this idea, with Kelly Edwards noting that "we all want to accelerate science, we all want to get to health impact, and we all are struggling with the accrual problem, the patient recruitment problem, we're all struggling with funding. So why not include clinical proof of concept?" Eck pointed out, though, that if the proof of concept succeeded, the drug would immediately become generic with no one to pay for phase III development.

Martin Yuille observed that the Innovative Medicines Initiative (IMI) in Europe has an operational way of defining the boundary between precompetitive and competitive. People from different companies formulate particular research topics, which then generate responses from academic consortia to work with industry on the topics. Issues such as IP protections are handled by the industry group, so they are no longer issues by the time the collaboration begins.

Sally John agreed that the IMI model has advantages, because industry can collaborate on what the bottlenecks are and make in-kind contributions to a project, which enables it to be a much more active participant. However some of the calls for precompetitive collaborations have been less successful than others, and some issues still need to be overcome as a collaboration proceeds. As Aled Edwards pointed out, this would include reevaluating the prohibition of an applicant sitting down to develop the plan in conjunction with the potential collaborating industry. Yuille responded by saying that the IMI is modifying its procedures on the basis of previous experiences, so that problems that have arisen are trying to be corrected. "It's an ongoing process of trying to improve what you're doing."

Stephen Friend asked specifically what needs to be changed to move the boundary between precompetitive and competitive R&D. Are the issues legal, ethical, economic, institutional, or cultural? "How do we exit the world that we're living in and get to this world that we might want to live in?"

Clayton emphasized that other areas of biology have already made this transition. The Human Genome Project and the Human HapMap Project both had to negotiate the terms of what was precompetitive and what was competitive. "It's a good idea to learn from past experience." It also helps to have strong leaders, she said.

MOVING FORWARD

Neil said that leadership has to come from many sources: policy makers, the patient advocacy community, the FDA, Health and Human Services, the Centers for Medicare and Medicaid Services, and other regulatory agencies. "All these people need to be at the table to talk about how we're really going to get after this. Because this really matters. It matters to public health, it matters to issues of access and affordability of care, . . . an aging population that's going to need more of what we can deliver, and how we're going to be able to continue to be competitive as a country."

The challenge with drug development, said Terry, is to move collaboration to the point that it is dealing with products that could change lives. This requires leadership, by both NIH and the pharmaceutical industry. She suggested that "it has to be NIH, with probably a pharma leader who is visionary and willing to risk a great deal, standing up and saying, 'We are going to change the culture.'" A participant noted that "if NIH and [the pharmaceutical industry] got together . . . the academic research enterprise will follow."

Thomas Insel challenged the Roundtable on Translating Genomic-Based Research for Health to create a vision that can be shared by all stakeholder groups, including patient groups. Many resources can be shared beyond data. For example, "there are lots of wonderful small molecules, and lots of drugs that people try that don't work, that pharma has on the shelf. . . . Often it's because they have some kind of off-target indications, but their off-target indication may be exactly the on-target indication for somebody somewhere else." Enabling the sharing of other kinds of resources could allow the development of a "safe haven" and a different culture which could then forge a path for more controversial items. Eck agreed and pointed out that in-house software tools may be easier to make available because there are fewer obstacles to overcome in order to do so. "There's no competitive disadvantage to us in making these tools widely available," he said.

SHARING BIOSPECIMENS AND DATA

To enable the sharing of biospecimens and data in a precompetitive manner, several potential paths were espoused by participants. Terry suggested that it may be necessary to have NIH make it a requirement of academic investigators to deposit these items into a public commons. Edwards suggested as an alternative, the negotiation of what will be shared on a project by project basis. Eck pointed out that a neutral third party may be required to decide which materials should be open access and which should remain under wraps. John said that PIs should have a say over what hap-

pens to their samples. "The people who collected the samples, who have done all the work, who collected all the baseline data, they are the people who will be best able to interpret results." Ellen Wright Clayton reminded the group that "one of the things that needs to change is the idea that what's yours is mine and what's mine is not yours." People have a tendency to say that they "own" certain objects or ideas, but a better model than an ownership model, according to Clayton, is a stewardship model in which institutions have responsibilities toward samples and the donors of those samples.

Faculty members and their students are stakeholders in these decisions, Frazier said. They have to benefit for them to accept whatever model is adopted. Kelly Edwards agreed, saying that "it doesn't help us to have good guys and bad guys. I think we have to be honest about the history that we're coming from and focus on the process of getting [samples and data] shared. The present task is to work toward equity, if not equality, in sharing benefits and risks "so that there's something in it for everyone."

FINAL THOUGHTS

Eck summed up by identifying the ingredients needed to move forward, including incentives, appropriate forms of consent, funding, governance, a focus on specific topics to engage upon, and strong leadership. Spencer added that the leader must convince the government to engage in a cooperative effort that will shorten the time and reduce the cost of bringing a new drug to market. Flexibility in program design is also a key element he said. "If you set a program that isn't exactly right, you've got to be willing to make a change and sell it to the people who funded you."

Neil reminded the group that just before he was a medical student, the cure rate for childhood leukemia was about 15 percent. Today it is 85 percent. The tools and drugs available today can produce that kind of progress in many other areas through a coordinated effort among academic centers, NIH funding, and industry, he said. "We need to remember what we can do when we get together with leadership, with the contemporary tools that we have, and with the highly targeted therapies that we have now. If we can address the infrastructure, the regulatory science, and the coordination, it would be very achievable to make significant progress on many of the big diseases that face us."

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Appendix A

Workshop Agenda

Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development

July 22, 2010

The Keck Center, Room 100
500 Fifth Street, N.W.
Washington, DC 20001

MEETING OBJECTIVE

To explore relevant issues related to developing a cultural, legal, and behavioral framework of collaboration that enables biospecimen and data sharing.

- What are the critical factors necessary for a successful collaboration?
- What lessons can be learned from existing collaborations?
- What are the challenges that exist and potential ways to overcome them?

8:00-9:00 A.M. **WORKING BREAKFAST**

9:00 A.M. **PUBLIC WORKSHOP BEGINS**

9:00-9:10 A.M. **Welcome and Introductory Remarks**
Geoffrey Ginsburg, Director, Center for Genomic Medicine, Institute for Genomic Sciences & Policy, Duke University

9:10-9:55 A.M.	**EXTENDING THE SPECTRUM OF PRECOMPETITIVE ONCOLOGY BIOMEDICAL RESEARCH: A SUMMARY**
	Moderator: *Martha Turner, American Nurses Association*
9:10-9:35 A.M.	**Lessons Learned** *Stephen Friend, President and Chief Executive Officer (CEO), Sage Bionetworks*
9:35-9:55 A.M.	**Discussion**
9:55-11:30 A.M.	**REQUISITES FOR SUCCESSFUL PRECOMPETITIVE COLLABORATION**
	Moderator: *Sharon Terry, Genetic Alliance*
9:55-10:15 A.M.	**The Architecture of Collaboration** *William J. Spencer, Chairman Emeritus, SEMATECH*
10:15-10:35 A.M.	**Requisites from the Pharmaceutical Industry** *Aidan Power, Vice President and Global Head of Molecular Medicine, Pfizer Inc.*
10:35-10:50 A.M.	**BREAK**
10:50-11:10 A.M.	**Requisites from Diagnostic Companies** *Marcia Eisenberg, Senior Vice President, LabCorp*
11:10-11:30 A.M.	**Requisites from Academia** *Neal Cohen, Vice Dean, School of Medicine, Professor of Anesthesia and Perioperative Care and Medicine, Director of International Medical Services, University of California, San Francisco*
11:30 A.M.-12:30 P.M.	**WORKING LUNCH**

12:30-2:05 P.M. **FRAMEWORK OF COLLABORATIONS WITH THE PHARMACEUTICAL INDUSTRY**

Moderator: *Aidan Power, Pfizer Inc.*

12:30-12:50 P.M. **Public–Private Partnerships with NIH or Government**
Thomas Insel, Director of the National Institute of Mental Health, National Institutes of Health

12:50-1:10 P.M. **Advancing Technological Achievements Through Collaboration**
Christopher Beecher, Research Professor, Michigan Center for Translational Pathology, University of Michigan

1:10-1:30 P.M. **Open Access Partnerships**
Aled Edwards, Director and CEO, Structural Genomics Consortium; Professor, Department of Medical Biophysics, University of Toronto

1:30-1:50 P.M. **Access to Large-Scale Data Networks**
Stephen Friend, President and CEO, Sage Bionetworks

1:50-2:05 P.M. **BREAK**

2:05-4:05 P.M. **BIOSPECIMENS**

Moderator: *Geoffrey Ginsburg, Duke University*

2:05-2:25 P.M. **Sustaining Access to Biospecimens**
Martin Yuille, Reader in Biobanking, Co-director, Centre for Integrated Genomic Medical Research, University of Manchester

2:25-2:45 P.M. **Developing Common Biorepository Infrastructures**
Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research, National Cancer Institute

2:45-3:05 P.M. **Linking Health Outcomes Data to Biorepository Samples**
Cynthia Helphingstine, President and CEO, Fairbanks Institute for Healthy Communities

3:05-3:25 P.M. **Creating a National Virtual Biospecimen Bank**
Lorraine Q. Frazier, Nancy B. Willerson Distinguished Professorship, Assistant Dean & Department Chair, Nursing Systems, Professor, Department of Nursing Systems, University of Texas Health Science Center at Houston

3:25-3:45 P.M. **Opportunities and Challenges of Clinical and Genetic Data Access in the Pharmaceutical Industry**
Sally John, Head of Human Genetics, Molecular Medicine, PharmaTherapeutics Research, Pfizer Inc.

3:45-4:05 P.M. **Ethical Challenges for Biospecimen and Data Sharing**
Ellen Wright Clayton, Rosalind E. Franklin Professor of Genetics and Health Policy; Director, Center for Biomedical Ethics and Society, Vanderbilt University

4:05-5:05 P.M. PANEL DISCUSSION

4:05 - 5:05 P.M. **Developing a cultural, legal, and behavioral framework of collaboration that enables resource sharing in order to accelerate genomics-based drug and diagnostic product development**

Moderator: *Stephen Eck, Eli Lilly and Company*

Panelists:

Ellen Wright Clayton, Rosalind E. Franklin Professor of Genetics and Health Policy; Director, Center for Biomedical Ethics and Society, Vanderbilt University

Kelly Edwards, Associate Professor, Department of Bioethics and Humanities, University of Washington School of Medicine
Lorraine Q. Frazier, Nancy B. Willerson Distinguished Professorship, Assistant Dean & Department Chair, Nursing Systems, Professor, Department of Nursing Systems, University of Texas Health Science Center at Houston
Geoffrey Ginsburg, Director, Center for Genomic Medicine, Institute for Genomic Sciences & Policy, Duke University
Garry Neil, Corporate Vice President, COSAT, Johnson & Johnson
William J. Spencer, Chairman Emeritus, SEMATECH
Sharon Terry, President and CEO, Genetic Alliance

5:05-5:30 P.M. **SUMMARY AND CONCLUSIONS**

Geoffrey Ginsburg, Director, Center for Genomic Medicine, Institute for Genomic Sciences & Policy, Duke University
Stephen Eck, Vice President, Translational Medicine & Pharmacogenomics, Eli Lilly and Company
Aidan Power, Vice President and Global Head of Molecular Medicine, Pfizer Inc.
Sharon Terry, President and CEO, Genetic Alliance

B

Speaker Biographical Sketches

Christopher Beecher, Ph.D., is research professor at the Michigan Center for Translational Pathology, University of Michigan. The research focus of the Beecher laboratory is centered on the continued development of the science of metabolomics. In this newest of the "omics" sciences, establishing methods for higher sensitivity, resolution, and reproducibility and algorithms for data handling and data generation are areas of ongoing exploration. The lab actively collaborates with a variety of researchers to find novel experimental systems that may benefit from a metabolomic analytical approach and will provide new avenues for metabolomic exploration. The Beecher recipe for a metabolomic platform is (1) a mass spectrometer-based analytical that is (2) well integrated into a (3) fully automated sample preparation operation. A full integration requires a sample flow through the platform that is fully directed by a custom-built laboratory information system (LIMS) and a second fully automated informatics system for processing information generated within the platform. Because of the high level of integration and automation, one can put in place a relentless program for error reduction and improvement. Dr. Beecher holds a B.A. in anthropology (New York University), M.S. in biology (New York University), and Ph.D. in pharmaceutical sciences–natural products chemistry (University of Connecticut). He began his research into the high-throughput chemical characterization of complex mixtures while on the faculty of the University of Illinois, College of Pharmacy (1985), where he held the position of associate professor. He was the editor of the NAPRALERT database from 1990 to 1998 and editor-in-chief of the *International Journal of Pharmacognosy*, and he served as a founding member of the Functional Foods Program of

the University of Illinois. In 1997 he was invited to continue this research in the laboratories of Bristol-Myers Squibb and Ancile Pharmaceuticals. His focus shifted from secondary metabolism to primary metabolism with the establishment of the first metabolomics platform in America at Paradigm Genetics from 2000 to 2002, and in 2003, he founded two metabolomics-based companies: Metabolon, Inc. (a company that has focused platform technologies on human health care) and Metabolic Analyses, Inc. (a company that has focused on the informatics issues associated with metabolomics). Dr. Beecher compiled the first human metabolome in 2002 at Metabolic Analyses and has been working toward the integration of metabolomic, proteomic, transcriptomic, and genomic data. In addition to his primary appointment at the University of Michigan, Dr. Beecher serves as an adjunct professor at George Mason University and is an affiliate of the National Institute of Statistical Sciences. He holds many patents and publications in the areas of metabolomics and natural products chemistry.

Ellen Wright Clayton, M.D., J.D., received a bachelor's degree from Duke, a master's degree from Stanford, her law degree from Yale, and her medical degree from Harvard. A member of the Vanderbilt faculty since 1988, she is currently the Rosalind E. Franklin Professor of Genetics and Health Policy and co-director of the Center for Biomedical Ethics and Society at the Vanderbilt University Medical Center. She is also professor of pediatrics and professor of law. At Vanderbilt, she directs the Law Emphasis Program and teaches in the patient, profession, and society course in the medical school and teaches the interdisciplinary course in bioethics and law in four schools of the university. Dr. Clayton has focused primarily on issues surrounding the ethical, legal, and social implications of advances in genetics and genomics as both a scholar and a policy maker. She has served on Tennessee's Genetics Advisory Council since the early 1990s, has participated in numerous policy and academic groups that have considered newborn screening, and is currently conducting research on the impact of false positive results in newborn screening. She has been very involved with the Human Genome Project in the United States, serving as a member of the National Advisory Council for Human Genome Research and more recently as co-chair of the Ethical, Legal, and Social Implications Working Group of the International Haplotype Mapping Project. She has also been very involved in ethical issues raised by genetics and genomics research, working with investigators and deliberative bodies around the world. She has been instrumental in the development of Vanderbilt's DNA biobank and is currently co-chair of the Consent and Community Consultation Working Group of the eMERGE consortium, which is studying the use of electronic medical records in genome-wide association studies. She has also written about a variety of issues regarding children's and women's health.

A member of the Institute of Medicine since 2006, she has served on the Health Sciences Policy Board, on its Advisory Council, and on several IOM committees, chairing committees to evaluate Title X family planning and to evaluate the safety of vaccines.

Neal Cohen, M.D., is professor of anesthesia and medicine and vice dean for the University of California, San Francisco (UCSF), School of Medicine. He also serves as the medical director of the International Service. Dr. Cohen received a B.A. degree from the University of Wisconsin, M.D. from UCSF School of Medicine, M.P.H. from the University of California, Berkeley, and M.S. in management from the Stanford University Graduate School of Business. Dr. Cohen is responsible for oversight and approval of all academic and clinical affiliations between the School of Medicine, other academic and clinical institutions, and industry, both nationally and internationally. He recently chaired the committee that developed the policy on industry relations and serves as chair for the task force that oversees the policy. He is currently working on the process for public disclosure of industry relationships for the University of California. Dr. Cohen was recently awarded the Lifetime Achievement Award from the American Society of Critical Care Anesthesiologists. Dr. Cohen has authored numerous articles and presented lectures on a wide array of topics related to the care of critically ill patients, practice management, and industry relations and their impact on innovations in health care, compliance, and regulatory affairs.

Carolyn Compton, M.D., Ph.D., is the director of the Office of Biorepositories and Biospecimen Research at the National Cancer Institute (NCI). In this capacity, she has leadership responsibility for strategic initiatives that include the Cancer Human Biobank (caHUB) project, the Innovative Molecular Analysis Technologies for Cancer program, and the NCI Community Cancer Centers project. She is an adjunct professor of pathology at the Johns Hopkins School of Medicine. She received her M.D. and Ph.D. degrees from Harvard Medical School and the Harvard Graduate School of Arts and Sciences. She is trained and board-certified in both anatomic pathology and clinical pathology at Harvard's Brigham and Women's Hospital. She came to the NCI from McGill University, where she had been the Strathcona Professor and Chair of Pathology and the pathologist-in-chief of McGill University Health Center from 2000 to 2005. Prior to this, she had been a professor of pathology at Harvard Medical School and the Massachusetts General Hospital, where she was the director of gastrointestinal pathology for 15 years. Dr. Compton has held many national and international leadership positions in pathology and cancer-related professional organizations. Currently, she is the chair of the American Joint Committee

on Cancer and a member of the Executive Committee of the Commission on Cancer. She has published more than 500 original scientific papers, reports, review articles, books, and abstracts.

Stephen L. Eck, M.D., Ph.D., joined Eli Lilly and Company in July 2007 as the global leader of Translational Medicine and Pharmacogenomics. Translational medicine ensures that the scientific concepts that underpin new medicines are used in the design of human clinical trials and that the molecular attributes of promising new medicines can be tested in patients. Pharmacogenomics seeks to understand how genetic differences among patients contribute to differences in drug effectiveness and safety. Together these disciplines can ensure the more effective use of drug development resources and the ultimate use of medicines in the most appropriate patient population. Dr. Eck has significant experience in drug development, having previously led several oncology and neuroscience drug development groups at Pfizer. He previously served as the Neurosciences and Oncology Clinical Site head at Pfizer's Ann Arbor facility. He subsequently lead a phase III oncology drug development team before being appointed vice president for translational and molecular medicine at Pfizer. Prior to joining Pfizer he served on the faculty of the University of Pennsylvania. Dr. Eck received his undergraduate training at Kalamazoo College (B.A.) and graduate training in chemistry from Harvard University (M.S., Ph.D.). He subsequently joined the Monsanto Company as a senior scientist conducting oncology drug discovery research. He later received his medical training from the University of Mississippi (M.D.). After internal medicine residency and hematology-oncology fellowship training at the University of Michigan, he joined its faculty before moving to the University of Pennsylvania as the Anne B. Young Assistant Professor of Cancer Research. At the University of Pennsylvania he was the director of the Cancer Gene Therapy Program and conducted basic and clinical research in cancer therapeutics.

Aled Edwards, Ph.D., is Banbury Professor of Medical Research at the University of Toronto, visiting professor of chemical biology at the University of Oxford, and chief executive of the Structural Genomics Consortium (SGC), an Anglo-Canadian-Swedish public–private partnership created to increase substantially the number of protein structures of relevance to human health available in the public domain, without restriction on use. Funded by industry, governments, and charitable foundations, the SGC accounts for more than a quarter of the world's output of human protein structures and more than 75 percent of the world's output of proteins from the parasites that cause malaria, toxoplasmosis, and cryptosporidiosis. Edwards believes that the discovery of new medicines would be most efficiently accomplished by performing many aspects of drug discovery research, from discovery to

clinical proof of concept, within precompetitive research consortia and by deemphasizing the perceived value of patents. Edwards was scientific consultant for the Canadian dramatic TV series, *ReGenesis*, and has founded a number of biotechnology companies.

Kelly Edwards, Ph.D., is an associate professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine and core faculty for the Institute for Public Health Genetics. She received an M.A. in medical ethics and a Ph.D. in philosophy of education from the University of Washington, Seattle. Her research and program responsibilities include serving as director of the Ethics and Outreach Core for the National Institute for Environmental Health Sciences (NIEHS)–funded Center for Ecogenetics and Environmental Health, as co-director of the Regulatory Support and Bioethics Core for the Institute for Translational Health Sciences (a Clinical, Translational, and Science Awards [CTSA] institution), and as lead investigator with the National Human Genome Research Institute (NHGRI)–funded Center for Genomics and Healthcare Equality. Her special interests include community-based research practices, biobank governance, environmental justice, everyday ethics in research practice, feminist and narrative approaches to bioethics, and integrating ethics into training programs, public conversations about science, and public policy.

Marcia Eisenberg, Ph.D., earned a B.S. in biology, a B.A. in psychology, and an M.S. in molecular biology from the State University of New York at Albany. She earned a Ph.D. in molecular biology from the University of Kentucky. Her experience includes work with the National Institute of Environmental Health Sciences. Dr. Eisenberg has been a member of the Federal Bureau of Investigation's (FBI's) Technical Working Group on DNA Analysis Methods, and she was an appointed member of the National DNA Advisory Board during its life span. She has been recognized and honored for her contributions to the advancement of forensic DNA testing. She currently holds certification in molecular genetics and molecular oncology, forensic DNA testing, and paternity testing from the New York State Department of Health. She has been involved with the development and validation of hundreds of clinical assays used for patient care during her 20+ year tenure at LabCorp and its predecessor company Roche Biomedical Laboratories. She has also developed and validated assays for clinical trial use and has participated in numbers of trials that were submitted to the Food and Drug Administration. She was initially hired to convert the then-current diagnostic testing to polymerase chain reaction-based testing, which at the time was a technology newly acquired by Roche. Dr. Eisenberg is currently a senior vice president and oversees test development, optimization, and automation for the company. She assists in review of new tests,

technologies, and platforms and works with partners to transform their intellectual property into viable diagnostic assays.

Lorraine Frazier, Ph.D., is the distinguished Nancy B. Willerson Professor of Nursing at the University of Texas at Houston Health Science Center (UTHSC-H) School of Nursing. She received a baccalaureate degree in nursing science from the University of Oklahoma. She received both her master's and her Ph.D. in nursing from the UTHSC-H School of Nursing. Her master's degree focused on adults and gerontology in the nurse practitioner program. During her doctoral studies she was awarded an Individual National Research Service Award from the National Institute of Nursing Research (NINR) at the National Institutes of Health (NIH) for the proposal "Predicting Hypertension Using Blood Pressure Reactivity." Following her doctoral program, she was a NIH fellow at the Summer Genetics Institute, a two-month intensive education program in genetics funded by the NINR at NIH. Postdoctorate education includes a 2-year postdoctoral fellowship funded by the NINR to study genetics and hypertension at the UTHSC-H Institute of Molecular Medicine for the proposal "Pharmacogenomic Studies of Human Hypertension." She was awarded a Mentored Patient-Oriented Research Career Development Award (K23) from NINR to support career development that allowed a research focus on patient-oriented research. The K23 award proposal entitled "Inflammatory Markers and Cardiovascular Patient Outcomes" focused on genetic factors and biochemical markers as predictors of risk in a large cohort of cardiovascular patients. As part of her K23 award, she completed a master's degree in clinical research with a focus on translational research at the UT School of Medicine. As a faculty member, she continues to study clinical design methods for clinical research in cardiovascular disease. The consistent theme throughout Dr. Frazier's program of research has been the exploration of biological and behavioral risk factors as predictors of outcomes in patients with cardiovascular disease. Her focus is on the genetic-environmental interaction of inflammation and depression on coronary outcomes in individuals with acute coronary syndromes and heart failure. Her patient population includes acute care patients at St. Luke's Episcopal and Ben Taub Hospitals. Dr. Frazier is the principal investigator on the 1R01NR010235-01A1 "Depressive Symptoms and Genetic Influences on Cardiac Outcomes," funded by NINR. She is the project director of TexGen Research, which supports multi-center, multi-institutional biobank development of clinical data and biological samplings from cardiovascular and cancer patients at the Texas Medical Center. She is also the director of the Center for Clinical and Translational Science (CCTS) BioBank at UTHSC-H. These biobank efforts currently have 135,000 biological samples and corresponding clinical data and incorporate eight hospitals and six univer-

sities. The University of Texas Clinical and Translational Science Award recipients (UTHSC-H/UT MDACC, UT San Antonio, and UT Southwestern) have identified the biobank effort as a priority for Texas CCTS collaboration. Dr. Frazier will direct the expanded biobank effort. Dr. Frazier is a fellow of the American Academy of Nursing, a fellow of the American Heart Association, and a Robert Wood Johnson executive nurse fellow. She holds memberships in numerous professional organizations.

Stephen Friend, M.D., Ph.D., is the president of Sage Bionetworks, a nonprofit foundation he co-founded in August 2009, based at the Fred Hutchinson Cancer Center to encourage the sharing of clinical-genomic data and models to generate representations of disease capable of driving new therapies and diagnostics (www.sagebase.org). He was previously a senior vice president at Merck & Co., Inc., where he led Merck's molecular profiling and then its cancer research, which in 2008 alone placed seven new oncology CMEs into clinical trials. Prior to joining Merck, Dr. Friend founded Rosetta Inpharmatics, which he led from 1997 until 2001, when he sold it to Merck for $600 million. Before that, he was recruited by Dr. Leland Hartwell to build the Fred Hutchinson Cancer Research Center's Seattle Project, an advanced institute for drug discovery. While there, Drs. Friend and Hartwell developed a method for examining large patterns of genes that led them to co-found Rosetta Inpharmatics in 2001. Dr. Friend also held faculty positions at Harvard Medical School from 1987 to 1995 and at Massachusetts General Hospital from 1990 to 1995. Before that, he worked at the Whitehead Institute where he led the team that cloned the first tumor suppressor gene while in Bob Weinberg's lab. Dr. Friend received his B.A. in philosophy, his Ph.D. in biochemistry, and his M.D. from Indiana University.

Geoffrey Ginsburg, M.D., Ph.D., is professor of medicine and director of the Center for Genomic Medicine. Previously, Dr. Ginsburg was with Millennium Pharmaceuticals in Cambridge, Massachusetts, where he was vice president of molecular and personalized medicine. At Millennium, Dr. Ginsburg was responsible for crafting strategy on the discovery of "biomarkers," genetic characteristics that measure the effects or progress of a disease or condition, and their use for clinical prediction and diagnosis. Dr. Ginsburg received both his M.D. and his Ph.D. degrees from Boston University. He completed his clinical and research fellowships in molecular cardiology at Beth Israel Hospital and at Children's Hospital in Boston. Dr. Ginsburg developed and directed the preventive cardiology service at Beth Israel Hospital in the late 1980s and has served on the faculty of Harvard Medical School since 1990. In addition to his role in the Institute for

Genome Sciences and Policy, he is a member of the faculty in the Department of Medicine at Duke University Medical Center.

Cynthia Helphingstine, Ph.D., is president and chief executive officer of the Fairbanks Institute for Healthy Communities, a not-for-profit organization utilizing the population of central Indiana in a novel longitudinal study that links biological specimens with clinical outcomes data from the nation's most established and data-rich clinical data repository to enable breakthrough translational research aimed at improving patient outcomes and reducing the financial, physical, and emotional burden of chronic diseases. An entrepreneurial executive, Dr. Helphingstine has a record of successfully bringing together diverse stakeholders to create companies and launch initiatives that impact health care research. Her experience ranges from product development and clinical research positions at Baxter Healthcare to translational scientific officer at BioCrossroads, Indiana's life science initiative, where she worked to accelerate the advancement of research discoveries at Indiana University from the laboratory to the marketplace. Dr. Helphingstine holds a Ph.D. in immunology and a B.A. in microbiology from the University of Missouri-Columbia and an M.B.A. from the Lake Forest Graduate School of Management in Lake Forest, Illinois.

Thomas R. Insel, M.D., is the director of the National Institute of Mental Health (NIMH). In this role, since 2002, he has led the nation's investment for research on the causes and treatments of mental disorders. His tenure at NIMH has been marked by a commitment to the problems of individuals and families with serious mental illness, with a focus on specific public health outcomes. In addition to his leadership of NIMH, Dr. Insel serves as the chair of the Interagency Autism Coordinating Committee for the Secretary of the Department of Health and Human Services. While trained as a physician (graduating from the combined B.A.-M.D. program at Boston University in 1974) and a psychiatrist (completing residency at the Langley Porter Neuropsychiatric Institute at the University of California, San Francisco, in 1979), Dr. Insel spent most of his scientific career as a basic neuroscientist focused on the molecular basis of complex social behaviors, such as social attachment. Prior to his current position at NIMH, Dr. Insel served as director of the Yerkes Regional Primate Center (1994-1999) at Emory University and founding director of the Center for Behavioral Neuroscience (1999-2002) in Atlanta, Georgia. He has published more than 250 scientific articles and four books, including *Neurobiology of Parental Care* (with Michael Numan) in 2003. He is a member of the Institute of Medicine (IOM) and a recipient of many awards, including the 2010 Ipsen Prize.

Sally John, Ph.D., joined Pfizer in 2007 and is currently the head of the Human Genetics Group within the Molecular Medicine organization. Dr. John's group focuses on applying human genetics to support drug discovery and development, from identification of new targets through to understanding genetic variability in drug response. Prior to joining Pfizer, Dr. John was a senior lecturer in genetic epidemiology at the University of Manchester, United Kingdom, where she built up a publication record in complex disease genetics. Dr. John has previous industry experience: at AstraZeneca she was responsible for inflammatory genetics and she established the statistical genetics group there. Her main focus of research has been in the area of inflammatory genetics, including rheumatoid arthritis and asthma, and also genetic epidemiology methods as applied to the analysis of complex traits. Dr. John gained a Ph.D. in molecular biology in 1994 from the University of Manchester, UK.

Garry Neil, M.D., is corporate vice president, Corporate Office of Science and Technology, Johnson & Johnson (J&J). In this role, Dr. Neil leads a team that catalyzes sustained growth for J&J by identifying and launching emerging technologies that underpin the creation of future businesses. Dr. Neil has broad experience in science, medicine, and pharmaceutical development. He has held a number of senior positions within J&J, most recently group president, Johnson & Johnson Pharmaceutical Research and Development (J&JPRD), where he was responsible for maximizing existing strengths and leveraging collective resources to bring innovative new molecular entities to market quickly and cost effectively. Through a number of new initiatives he helped transform J&J's pharmaceutical R&D to a much more capable and productive organization and helped recruit a number of top scientists. Under his leadership a number of important new medicines for the treatment of cancer, anemia, infections, central nervous system and psychiatric disorders, pain, and genitourinary and gastrointestinal diseases gained initial, new, and/or expanded indication approvals. Dr. Neil joined J&J in 2002 as senior vice president of Drug Development at J&JPRD. In 2005, he became president of J&JPRD, and in 2006, was promoted to group president. Before joining J&JPRD, Dr. Neil held senior-level positions with Astra Merck Inc., Astra Pharmaceuticals, AstraZeneca, and Merck KGaA. He has also held a number of posts at academic institutes including the Ludwig Institute for Cancer Research, the University of Toronto, the University of Iowa College of Medicine, and the University of Pennsylvania (adjunct). He also completed a postdoctoral research fellowship at the Research Institute of Scripps Clinic. He is a fellow of the American College of Physicians, a fellow of the American College of Gastroenterology, and a member of the American Association of Immunologists, and of the Society for Clinical Trials. He is a member of the Board

of the Reagan Udall Foundation and the J&J Development Corporation, and he is J&J's representative to, and vice chairman of, the Pharmaceutical Research and Manufacturers Association (PhRMA) Science and Regulatory Committee, vice chairman and treasurer of the PhRMA Foundation Board, a member of the Board of Trustees for the Robert Wood Johnson Medical School, a member of the Scientific Advisory Board of the Center for Advanced Biotechnology and Medicine (Rutgers), a member of the Executive Committee of the Biomarkers Consortium, and a member of the Board of Trustees of the Newark Boys Chorus School. He is also the 2007 discovery awardee of the American Geriatrics Society. He holds a Bachelor of Science degree from the University of Saskatchewan and a medical degree from the University of Saskatchewan College of Medicine; he completed his postdoctoral clinical training in internal medicine and gastroenterology at the University of Toronto.

Aidan Power, M.B., B.Ch., M.Sc., M.R.C.Psych., has been vice president and global head of Molecular Medicine since January 2008. Molecular Medicine represents a synthesis of all the emerging technologies and operations (computational science, imaging, pharmacogenomics, metabolomics, proteomics, physiological measurements, diagnostics) that form the scientific basis of emerging approaches to the development of personalized medicine. Graduating in medicine from University College Cork, Ireland, Dr. Power trained as a psychiatrist in England and joined Pfizer in the United Kingdom in 1993 to work on the antidepressant sertraline and the antipsychotic ziprasidone. In 2002, Dr. Power relocated to Pfizer Global Research and Development Headquarters in New London, Connecticut, where he headed clinical pharmacogenomics. Over the last year he has headed up molecular medicine, which has been integrating molecular studies across disease areas as well as developing diagnostics for critical programs in the Pfizer product pipeline.

William J. Spencer, Ph.D., D.Sc., retired as chairman of SEMATECH after earlier serving as president and CEO. Before joining SEMATECH, he was a group vice president and the senior technical officer of Xerox. He started his career at Bell Labs and held management positions at Sandia National Laboratories. He holds the position of research professor at the New Mexico School of Medicine and was a regents professor at Berkeley. He received the Regents Medal from the University of New Mexico; he is a fellow of the Polytechnic University of Brooklyn and of Kansas State University, where he received a Ph.D. in physics. He is a member of the National Academy of Engineering and a fellow of IEEE. He is a member of the athletic hall of fame and received doctor of science recognition from William Jewell

College. He and his wife Joan enjoy opera, the symphony, hiking, skiing, tennis, and just walking in the cities where they reside.

Sharon Terry, M.A., is president and CEO of the Genetic Alliance, a coalition of more than 600 disease-specific advocacy organizations working to increase capacity in advocacy organizations and to leverage the voices of the millions of individuals and families affected by genetic conditions. She is the founding executive director of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). She is at the forefront of consumer participation in genetics research, services, and policy and serves as a member of many of the major government advisory committees on medical research, including the FDA Cellular, Tissue and Gene Therapies Advisory Committee and the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. She is a member of the board of directors of the Biotechnology Institute and on the advisory board of the Johns Hopkins Genetics and Public Policy Center funded by the Pew Charitable Trusts. She is the chair of the Coalition for Genetic Fairness, composed of advocates, health care providers, and industry working to enact effective federal policy to prohibit genetic information discrimination. She is also chair of the Social Issues Committee of the American Society of Human Genetics. In 2005, she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping. Ms. Terry is a co-founder of the Genetic Alliance Biobank and serves as president of its board. It is a centralized biological and data (consent-clinical-environmental) repository catalyzing translational genomic research on rare genetic diseases. The biobank works in partnership with academic and industrial collaborators to develop novel diagnostics and therapeutics to better understand and treat these diseases. Along with the other co-inventors of the gene associated with PXE (ABCC6), she holds the patent for its invention. She co-directs a 19-laboratory research consortium and manages 52 offices worldwide for PXE International.

Martha Turner, Ph.D., R.N., is currently the assistant director of the American Nurses Association (ANA) Center for Ethics and Human Rights and an adjunct professor in the Department of Preventive Medicine and Biometrics, School of Medicine, Uniformed Services University of the Health Sciences (USUHS). She is co-director and lecturer for the public health ethics course (PMO 991). A recently retired Air Force Colonel, Dr. Turner was the consultant for health care ethics to the Air Force Surgeon General from 1998 until 2006. She represented the Department of Defense as an ex officio member of the Secretary's (HHS) Advisory Committee for Genetics, Health and Society (SACGHS). During the three years with SACGHS she became familiar with challenges associated with the development of new technolo-

gies and other scientific advances in genetics and genomics. On behalf of the ANA she reviewed and submitted comments on the draft reports "Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment, and Disease" (2006) and "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges" (2007). Her understanding of the challenges and opportunities for health professionals is demonstrated by her experience at the USUHS, where she teaches applied ethics courses in the M.P.H. and Ph.D.-Dr.P.H. programs. Additional activities have included membership on the TriService Nursing Research Program Advisory Council, various scientific review panels, the editorial board for the *Journal of Nursing Staff Development*, and the USUHS Institutional Review Board. Research, projects, and policy work have addressed pain management, end-of-life care, air evacuation of patients, care of those imprisoned, and other topics related to health care delivery in diverse environments. Dr. Turner has been participating on behalf of ANA at the American Society for Bioethics and Humanities, National Coalition for Health Professional Education in Genetics, and International Society of Nurses in Genetics meetings. Additionally, she has been collaborating with a national work group in planning and strategizing on implementation of the nursing core competencies approved and endorsed by the national nursing community.

Martin Yuille, Ph.D., is co-director at the Centre for Integrated Genomic Medical Research and reader in biobanking at the University of Manchester, deputy lead of Manchester Academic Health Science Centre Infrastructure and Technology, and associate coordinator of the European research infrastructure project preparation in biobanking. His primary research interest is in the development of research infrastructure that will best serve the emerging needs of biomedical research.