Integrating genomics technologies in health care: practice and policy challenges and opportunities

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Austin, M. J. Finley, and Thane Kreiner. Integrating genomics technologies in health care: practice and policy challenges and opportunities. Physiol Genomics 8: 33–40, 2002; 10.1152/physiolgenomics.00103.2001.—To consider broadly the potential impacts of new genetic technologies on clinical practice, a conference was convened at the Banbury Center of the Cold Spring Harbor Laboratories. Stakeholders from all sectors (industry, academia, basic and applied research, clinical genetics, medicine, law, patient advocacy, bioethics, and policy and regulatory) were brought together to explore areas of agreement and disagreement on how best to foster these changes and to guide future deliberations. We first examined the current state of technology development and potential applications. Next, current genetic applications in medicine were reviewed with the goal of identifying lessons learned and practices that can be applied to new applications. Last, the group explored regulatory and policy environments necessary for translating new technologies and knowledge into practice. We sought to better define and facilitate the necessary interaction between research, application, and policy and regulation. This perspective provides a summary of the collective thinking that emerged and a tool to identify issues for consideration and aid future discussions.

clinical genetics; DNA microarray; pharmacogenetics; genetic test; gene patent; human subjects

THE INTERACTION OF GENES with the environment is the basis of the human condition. Researchers and clinicians in industry, academia, private research institutes, and government laboratories are beginning to apply new genetic knowledge to diagnostic and pharmaceutical discovery, development and disease management. From its very inception, however, the Human Genome Project has engendered debate: the fate of “small” biology at the expense of the “big science”; how much of our destiny is in our genes; how to deal with the moral and ethical dilemmas posed by our new ability to collect extensive genetic information on individuals. Recognizing the potentially profound impact of new genetic technologies on clinical practice, a conference was convened February 25–28, 2001, at the Banbury Center of the Cold Spring Harbor Laboratories to explore areas of agreement and disagreement among stakeholders from all sectors on how best to foster and guide these changes. Participants at the conference1 were drawn from consumer groups, academic research, drug and diagnostic discovery and development, bioethics, law, policy, regulation, genetic counseling, and diagnostic and medical practice.

Participants welcomed the unique venue and variety of perspectives and opinions: it made our two and a half days together decidedly informative and prompted considered, thoughtful, lively exchange. Most, but not all, participants thought that genomics along with a number of other important drivers (e.g., demographics, new treatments and diagnostics, new approaches to delivery, and cost benefits) are shaping a new health care paradigm in which the genetic information will result in more precise, tailored care, including treatment options and selections for common, complex diseases. Participants agreed that most disease states, especially common ones, are heterogeneous in nature: different combinations of inherited genetic, environmen-

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tal, and behavioral factors result in the same clinical phenotype; perturbations in different pathways may produce the same end effect. Disagreement, however, arose as to our ability to develop the scientific know-how to dissect out the inherited genetic susceptibility factors in common, complex diseases. Participants did agree that genetic variation can be clinically significant in a variety of ways. Responsiveness to drugs can be influenced by the genotype of the host or the infectious agent through three distinct means: 1) Genetic polymorphisms in the host of all types (e.g., single nucleotide changes, gene deletions, etc.) can alter drug targets, transporters and/or routes of metabolism. These in turn can change actual target responsiveness, bioavailability and/or plasma concentration, all of which can affect efficacy and safety. 2) Somatic genetic changes, or acquired mutations, in the host can have a profound effect on malignant transformation and other types of pathology and can also influence the choice of drugs. 3) The ability to detect genetic differences among the same species of pathogen can improve antimicrobial therapy.

After examining the current state of technology and potential applications, we explored the role of policy and regulatory environments, looking both at impacts on research, development, and applications today as well as how they are shaping the future. From this broad-based dialogue we reached consensus that: 1) The challenges presented by genetics and genomics primarily occur within existing legal, ethical, and social concerns rather than creating new ones. 2) Discovery, applications, and policy constantly inform one another, and they must be considered as a whole system. Yet, the wide range of potential genetics and genomics applications, risks, and benefits preclude a “one size fits all” regulatory approach. 3) Efficient realization of potential benefits will require collaboration among industry, government, academia, patient groups, and professional societies, and education for all will be key. 4) Evolutionary rather than revolutionary change is occurring in all areas of discovery, application, and policy. This evolution is best guided through measured and thoughtful changes.

OVERVIEW

Technology and Discovery

An assortment of technologies is helping scientists discover genes, how allelic variations affect gene expression and gene product function, and how, in turn, these genetically based differences affect the development and manifestations of disease. Some of these technologies are also emerging as potential platforms for new diagnostics. For example, in a proof of principle experiment using DNA microarrays that simultaneously measure the expression levels of thousands of genes (1), clear and accurate expression pattern differences were demonstrated between two closely related leukemias allowing for their differential molecular diagnosis. The treatment paths for these two leukemias, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are radically different, one requiring long-term chemotherapy and the other a bone marrow transplant. Other DNA microarray experiments suggest unique gene expression patterns are associated with a wide range of disorders and conditions such as alcohol sensitivity, diabetes and obesity, aging and muscular dystrophy. Although much work remains to validate and confirm such results, the knowledge gained through these studies is identifying new biomarkers and therapeutic targets. This information is opening up new avenues of research into pathophysiology and leading to other potential treatment strategies.

DNA microarrays are also being used for large-scale genotyping to assist in the discovery of genetically determined inherited differences in how individuals respond to drugs. In fact, genotyping of common drug metabolism enzymes on microarrays is already being used to detect differences in drug metabolism. Numerous alleles, particularly in the CYP2D6 pathway, are known to affect the metabolism of major classes of drugs currently on the market, including antihypertensives and antidepressants. These avenues of research will aid in guiding development decisions as well as leading to new drugs and dosing regimes that will ultimately reduce adverse events and improve treatment efficacy. Understanding drug metabolism genotypes can also help avoid or modulate drug-drug interactions. It is important to note, however, that drug safety and efficacy are affected by environmental factors such as patient compliance, nutrition and other compounds to which the patient may be exposed. Further research is needed on genetic-environmental interactions and to determine whether genotyping or phenotyping will be the best method for assessing patients’ likely drug response before making a drug prescription decision.

Single nucleotide polymorphisms (SNPs) are useful as markers for population studies and may provide the basis for detecting common variants that affect disease susceptibility. A public private consortium was initiated in 1999 to identify SNPs throughout the human genome. It is known that some rare alleles confer significant susceptibility to common disease but only account for a small fraction of those who develop the diseases (e.g., BRCA1 and BRCA2 in breast cancer). Beyond these rare instances, the use of SNPs to extend genotyping analysis to identifying susceptibility alleles to common causes for complex diseases remains unproven and controversial. Some participants argued that even if high-frequency alleles for common diseases could be identified, their low predictive value would render them virtually useless for clinical practice. Others contend that by using appropriate, well-characterized populations, validated SNPs, and statistically sound study designs coupled with more cost-effective genotyping technologies, positive benefits are achievable.

Because this area of research, sometimes referred to as “translational,” reflecting the translation of the
human genome sequence to useful medical applications, is highly uncertain, it is unclear who should fund these large-scale experiments. Public domain sequencing efforts have provided a repository of knowledge for the common good, but not all scientists agree that a massive attempt to associate SNPs with common, complex diseases will be similarly fruitful. Some argue that the likelihood of finding associations is so small that public funds would be better spent in other avenues of research. They further contend that it is the commercial sector that will benefit (e.g., through the development of new drugs, treatments, and diagnostics), if such associations happen to be found; therefore, the search for genes related to common diseases should be funded by industry. Moreover, this investment benefits the private sector’s social role of developing and producing innovative health products. However, others argue that making the sequence useful for elucidating disease mechanisms is likely to benefit basic research in all sectors and ultimately public health, and government funding could accelerate this process. Also given the risk profile of the science, only entities not concerned with profit will be willing to make the investment on a sufficiently large scale to have a significant probability of success. Thus the role of government vs. the private sector in translational research stands out as a key challenge in further exploration of genetic variation as it relates to common, complex conditions.

No matter what the sources of funding, a number of other challenges remain to expand and fully exploit the genetic information acquired via new technologies. Information processing and mining to transform raw data into knowledge remains a significant challenge. Although we may have lowered the barriers to exploring genotype, we still must establish better methods to obtain and analyze information from the environment. Also required are the following items: prospective, statistically valid studies; considerations of cost benefit and long-term value; and timely regulatory approval. It was agreed that rigorous phenotyping, appropriate population ascertainment and careful study design are critical for success. For many of these studies to be efficient and meaningful, designs supporting long-term, broad, comparable, and often observational rather than hypothesis-driven research are required. The long-term nature and “open questions” aspects of this research have raised concerns about participants’ ability to provide informed consent. Consequently, translational research will benefit from clear guidance balancing micro- and macro-ethical concerns and promoting consistent standards and comparable studies.

Applications and Delivery

The genome project has vastly accelerated gene discovery for Mendelian disorders and is elucidating pathways and informing target selection for therapeutic development. As this research progresses, the shortest term impacts of discovery and new technologies will likely influence diagnostics and therapeutics in four health care areas: 1) classic monogenic inherited disorders; 2) drug safety and efficacy; 3) somatic genetic changes involved in cancer, metabolic disorders, and other diseases; and 4) genetic contributions to complex diseases. Applications will likely come in the first three areas before we see major inroads in predicting and preventing complex diseases based on genetic knowledge. Also, although we expect further elucidation of alleles responsible for monogenic disorders, therapeutic development for these disorders remains a daunting biological challenge.

Monogenic inherited disorders. Most Mendelian disorders are relatively rare, and public funds for studies are essential to fostering gene discoveries, development of diagnostic tests and seeking therapeutic remedies. Effective management of Mendelian conditions, often presenting in infancy, will continue to require prompt recognition by primary care providers. The use of family history in conjunction with clinical findings will enable this prompt recognition. When primary care providers cannot make diagnoses, they must be able to stabilize the patient, if required, and make appropriate referrals. Specialists will manage specific problems with medical geneticists and counselors providing diagnostic assistance and patient and family counseling and consultation as well as long-term care. It is thus critical that genetics education enhances the ability of health care providers to recognize high-risk situations for Mendelian conditions. Single gene and chromosome disorders will continue to present opportunities and challenges with respect to population and newborn screening, carrier detection, predictive testing, and prenatal and confirmatory diagnosis.

Pharmacogenetics. A great deal is already understood about the effects of metabolic and receptor variation for drug treatments of complex diseases. Yet, this information is rarely applied in clinical practice. Why? The body of knowledge of drug metabolism has grown steadily. We know that metabolic differences affect a large number of drugs on the market. However, prospective studies are still needed to quantify and validate the effects so that drug and dosage options can be fully informed. Also, because of regulatory concerns, drug metabolism data has primarily been focused on eliminating drugs from the pipeline rather than rescuing compounds. If this knowledge is applied prospectively, then a wider variety of both compounds and dosages may fill the pharmaceutical arsenal. Pharmaceutical companies are already changing their research and development efforts, recognizing that no one drug may be safe and effective in all patients with a given disease. Both treatment improvements and reduced adverse events are the ultimate goals of this new approach to drug discovery and development. If pharmacogenomics proves fruitful, then testing patients for the genetic basis of their drug responsiveness before treatment is initiated may become common practice, particularly when empirical determination of patient response takes a long time and/or threatens the pa-
tient’s well-being. Additionally, getting the right drug to the right patient at the right time will produce cost and social benefits. Both development and clinical application hurdles will have to be addressed, however, for patients and the health care delivery system to profit from knowledge of metabolic variation. As tailoring of drug treatments becomes more prevalent, physicians will require more training to ensure optimal therapeutic prescriptions. Information management will become crucial; fast, efficient, reliable systems for providers to access necessary information in the course of care delivery will be essential.

**Somatic mutations and gene expression profiling.**

Both gene expression profiling and determination of somatic mutations can be carried out in any tissue, but their diagnostic and treatment applications will most likely be limited to lymphoblasts, tumors, and other easily definable, accessible sample sources. It is unlikely that somatic mutations will be practically useful in predictive testing for some time, due to tissue acquisition challenges and the currently limited understanding of their role in the etiology of diseases. Challenges for oncology applications include unraveling the pathways involved in cancer genesis and progression, elucidating mechanisms of interaction between tumors, the environment, and potential therapeutic options, and obtaining sufficient quantities of the tumor vs. normal tissue to detect the causative changes. The simplest applications of defining genetic roots may be reducing such changes to small subsets of common clinically useful biomarkers that can be assayed with existing diagnostic platforms such as immunohistochemistry. New diagnostic platforms are also anticipated based on tumor genotyping and gene expression monitoring. These types of genetic tests will not present the same ethical concerns as observing inherited mutations or polymorphisms, unless these molecular phenotypes can be shown to reflect underlying germline mutations.

**Complex diseases.**

In applying genomics technologies, we must bear in mind that data does not equal knowledge, and knowledge, while it will always inform research, does not always translate into useful clinical applications. This is universally true, but is particularly relevant to common complex diseases. As our understanding of the role of genetics and the use of gene-based markers extends to complex multifactorial disease, primary care providers will have to learn how to recognize patients who are at higher than general risk, usually by taking a careful family history, and who might benefit from predictive testing and preventative care. When referral is appropriate, and desired by the patient, specialists, such as oncologists and neurologists, will assist the primary care provider in management, with genetic specialists aiding in interpretation of test results, including family history, along with advising, counseling, and managing patients. It will be particularly important for physicians and for patients to understand the probabilistic nature and predictive value of tests for common diseases. This will be complicated if multiple low-frequency alleles and/or low-penetrance alleles are involved. The contribution of environment, including lifestyle choices such as diet and exercise, are recognized as critical elements in health maintenance. The issue of noncompliance, even when we know “what’s good for us,” was raised as a question relating to the cost-benefit of certain medical interventions and treatments. Choosing a test vs. simply recommending and adopting preventative measures such as dietary or other lifestyle changes will need to be carefully evaluated.

**Genetic specialists.**

The role and importance of genetic specialists and counselors and genetic counseling practices will be shifted and amplified as a result of these potential new genetic applications, particularly when genetic knowledge has clear relevance to others and/or treatment options are unavailable or radical. Geneticists and counselors will continue to serve as primary interfaces with patients and families affected by Mendelian, chromosome, and other congenital disorders. Moreover, as genetic tests extend beyond today’s stronghold of pediatric, prenatal and carrier testing, counselors will also function as consultants advising and educating others in the delivery system as well as a wider range of patients. This is already occurring in oncology. Additionally, standard frameworks of nondirective counseling may need to be revisited in some cases when diagnostic and treatment options are clearly defined. Genetic counselors, though, are few, and current reimbursement practices appear to severely undervalue their services and role in the total health care equation. Funding for genetic counselor training programs and evaluation of the health care billing practices is thus critical. Genetic counselors are nationally certified by the American Board of Genetic Counseling (ABGC) and, prior to 1993, were certified by the American Board of Medical Genetics. However, genetic counselors historically were not licensed, and this continues in most states, which significantly limits billing for their services. In September 2000, California became the first state to license genetic counselors. Many hope other states will follow California’s lead.

**Policy and Regulation**

One of the landmark characteristics of the Human Genome Project is the dedication of 3–5% of the research funds for exploration, evaluation, and recommendations on the ethical, legal, and social issues surrounding elucidation of the genome and genetic information. The farsighted decision to fund these studies has greatly advanced thinking on a number of critical areas, which in turn influences the formulation of public policy and regulations. Our discussion focused on five major policy areas of particular concern: 1) use of human subjects; 2) regulation of genetic tests; 3) gene patenting; 4) the special needs of rare disease sufferers; and 5) education.

**Human subjects.** Our current system for the protections of human subjects in research is undergoing
review and restructuring. The vision of the new Office of Human Research Protections (OHRP) is to move away from the Institutional Review Board as a wall between research investigators and the research subjects to a new system that puts subject protection as its central focus. This novel approach strives to integrate the accountability and responsibilities of sponsors, investigators, IRBs, and institutional administrations to ensure that they are working in concert to protect the interests of human subjects (Fig. 1).

This change, already underway, is fundamental to all human subject-based research. By applying a simplified oversight process that offers greater flexibility and accountability to organizations, the benefits of new knowledge can be more easily realized while optimizing protections for participants. The OHRP is assessing ways to streamline processes to enhance both efficiency and protections. One such suggestion is to centralize some IRB functions to better address large multi-center projects. Regardless of the final structures, it is important to ensure all IRBs have the expertise and resources sufficient to review genomics-related protocols.

Restructuring is being facilitated through the National Human Research Protections Advisory Committee. This diverse committee of 17 highly qualified representatives from the broad human research community (and 20 ex officio members from federal agencies and offices involved in human research) is charged with providing expert advice and recommendations to the Secretary of Health and Human Services, the Assistant Secretary for Health, the Director, OHRP, and other departmental officials on a broad range of issues and topics pertaining to or associated with the protection of human research subjects. The Committee held its first meeting in December 2000 and through formation of workgroups has already initiated efforts to address a number of human subjects’ protections issues (e.g., management of conflicts of interest, protection of children in research, and genetics research and collection of family history).

There are a number of human subjects research issues indirectly and directly relevant to genetics, genomics and pharmacogenomics that need to be addressed. Even though genotypes are individual, genetics research and knowledge also serve a community purpose and thereby challenge our concepts of duties and protections. Currently, two sets of federal regulations apply to human research; both are based on the “Belmont Report”: In the case of privately sponsored clinical trials, 21 CFR parts 50 and 56 govern human subjects oversight, and 45 CFR part 46 (or the agency-specific equivalent under the so-called “Common Rule”) applies for federally supported human research. This distinction between sponsorship and type of research allows for some types of privately supported research (e.g., privately conducted human reproduction assistance research) to be conducted without IRB review, approval, and oversight. This regulatory gap needs to be filled, particularly as more basic human genetics research is being privately funded and conducted. The Belmont Report also recognizes the importance of distinguishing between research and clinical practice. In the study of human genetics, it can be particularly difficult to draw the line between information and knowledge that only has research utility and information and knowledge that has clinical utility. Genetics research participants must be protected from misuse and inappropriate disclosure of data before clinical utility is proven and accepted. Issues of genetic privacy are already receiving congressional attention in the current administration.

**Regulation of genetic tests.** The Secretary’s Advisory Committee on Genetic Testing (SACGT) was chartered in 1998 to assess and ensure safe and effective oversight of genetic tests. The SACGT comprises 13 members and 7 ex officio members, and its federal advisory committee structure embodies involvement of federal agencies that might later implement rec-
ommendations by policy changes. The SACGT defines a genetic test as follows: “an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes. The purposes of these genetic tests include predicting risks of disease, screening of newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. Tests that are used primarily for other purposes, but that may contribute to diagnosing a genetic disease (e.g., blood smear, certain serum chemistries), would not be covered by this definition. Also excluded from the definition are tests conducted exclusively for forensic identity purposes.”

The SACGT’s recommendations, submitted to the Secretary of Health and Human Services in July 2000 and subsequently endorsed by Secretary Shalala, call for enhanced oversight and Food and Drug Administration (FDA) approval of all genetic tests. At present, FDA actively regulates genetic tests marketed as kits, but not tests marketed as laboratory services, or home-brews. SACGT, with FDA, is developing policies for setting priorities and review standards to minimize delays in genetic test development and marketing while ensuring the safety and efficacy of all tests. Adequate support for FDA to carry out its expanded role will be essential. SACGT also calls for legislation to prevent discrimination based on genetic information, educational efforts for the public and physicians, measures to ensure access to genetic tests, and importantly, continued public involvement in discussions. Their full report, Enhancing the Oversight of Genetic Tests, is available at: http://www4.od.nih.gov/oba/sacgt/gtdocuments.html.

Patenting. Although it is broadly accepted that DNA inventions are patentable and that these patents are critical for bringing innovations into practice, questions of how best to apply “gene” patents have lingered. For example, some contend that DNA patenting may increase the costs of genetic tests, potentially hampering access. They argue that compulsory licensing may be necessary to ensure test availability. Others have stressed the importance of maintaining our current patent system while providing guidance appropriate to DNA-based patents. The US Patent and Trademark Office (PTO) recently issued new guidelines for gene patents that add a third prong “substantial” to the standard utility test of “specific and credible.” This third prong means that the claim must be a real-world claim, one that offers a specific benefit to society. “Throwaway” utilities, such as using a gene or portion of a gene as a shampoo additive are excluded. This decision by PTO reinforces the social contract represented by the patent system, which gives the patent holder a period of exclusivity in exchange for offering an invention that benefits society. As our understanding of what truly constitutes a DNA-based invention evolves, a delicate balance between access and incentives for investment must be achieved.

Some 20,000 DNA fragment patents have already been issued by the PTO. In cases where multiple genes or alleles may affect the susceptibility of an individual to disease or alter drug efficacy or safety, it may be overly burdensome for test providers to reach commercially reasonable gene patent licensing terms. A consortium approach may be necessary for some commercial development applications. One concept proffered is that employed by the music industry: assignable rights are centralized, and copyright holders are paid based on an audit of actual play time, or music usage.

Rare disorders. Commercial development of tests for rare disorders poses a serious challenge. Because the market size is small, the economic incentives for both therapeutic and diagnostic development are often insufficient without subsidies. Furthermore, dedication of the bulk of public funding to common diseases can make it difficult for academic researchers to explore rare, inherited disorders, despite the fact that some such discoveries elucidate basic biological pathways relevant to common disease. Since the economic incentives for basic research in Mendelian disorders are low, it is all the more crucial that a reasonable portion of public funding be reserved for these studies. Additionally, special economic incentives for commercial test developers may be required to serve families suffering from rare disorders, along with the extent Orphan Drug Act to encourage therapeutic research and development.

Education. The topic of education was a recurring theme throughout the meeting. To effectively diagnose, treat, and manage patients, all care providers and specialists need to understand the role of genetics in both rare disorders and common, complex diseases. Patients need to become more “genetically literate” to make informed choices about tests and treatment options. We therefore emphasize the need for education, both of health care professionals and of the public at large. Creating a genetically literate society is a daunting task, but it is moderated in part by the recognition that many of the choices afforded by genetic information are nothing new. One day, these, too, will become standard practice. Just as individuals have learned to make health care and lifestyle decisions based on other medical information (e.g., cholesterol levels and ratios) with education, we will learn how to manage this new health care information. In fact, family history is often taken into clinical consideration. This is a form of genetic information, and for most conditions, understanding family history is important because it informs relative risks. Nevertheless, new technologies and clinical applications require new knowledge on the parts of its consumers and mediators. Tools and resources can be readily developed to transmit new knowledge, but necessary funds and will to devise
and implement training practice changes remain as challenges.

MANAGING THE FUTURE

In reviewing the 2-day discourse, two overarching themes repeatedly emerged. First, there is a natural tension between individual and subgroup risk-benefit ratio and the broader public’s risk-benefit ratio. Effective policy in all areas must balance this tension. Society’s function of focusing on the greater good can tolerate individual unmet need while striving to ensure that new products and practices are safe and effective. This broader risk benefit, however, often dominates and conflicts with individual and subgroup interests and the urgency of the affected. Second, information is the key product arising from and driving research, applications, and policy. Because our knowledge is continuously increasing, evolutionary rather than revolutionary change is occurring in each of these areas.

To conceptualize the meeting, we derived a model of the three interacting components (Fig. 2): 1) Technology and Discovery; 2) Applications and Delivery; and 3) Policy and Regulation.

Although it serves us to compartmentalize these processes and functions as they produce distinct outputs, they all also affect and produce information critical to each other’s functioning. Therefore, to operate effectively and efficiently, these units must be held in proximity. These units are dynamic, constantly interacting and informing; in fact, they represent continuums, not discrete units. While each component operates distinctly and constantly, albeit at varying paces, and all interact amongst the others, there must be sufficient pause and stability in the system such that actual products emerge and are delivered to those in need. These potential products are clear: they are the benefits of genetics and genomics as health care tools and information, and they are also the policies that encourage innovation and protect against misuse or abuse of information and unsafe, ineffective products and practices.

Just as health care will become more integrated and tailored, our regulatory and delivery processes need to be integrated and tailored. These processes must be flexible and responsive to variation in testing and treatment options, yet remain robust to assure the public at large and the individual safe and effective technologies and applications. Care delivery will continue to be provided by multiple people, including genetic counselors, nurses, pharmacists, general practitioners, and specialists, in varying roles and structures. Successful integration of genetics and genomics into health care will require the participation of all and will depend on the accuracy of the complex information to be utilized and conveyed. Different applications will have different impacts on individuals and their family members, and outcomes will depend on care available and extent of care required to manage health conditions. Reimbursement frameworks must recognize the long-term value of integrated approaches that better utilize tests and understand that a negative result often offers valuable information.

To identify and prioritize issues relevant to the various applications of genetics and genomics, a template was developed, which is published as a supplementary Appendix (see the Supplementary Material for this article, published online at the Physiological Genomics web site). This matrix is presented as a tool to aid us all (researchers, care providers, commercial developers, regulators, policy makers, and patients) in conceptualizing the issues we must consider and resolve as we apply the tools of genetics and genomics in health care practice. Some preliminary ideas are included in the matrix, but further input from and discussion among various stakeholders is essential.

Throughout our brief summary, we have remarked on potential mechanisms and challenges to ensure that the benefits of genetics and genomics are realized for both individuals and the public at large. A recent Institute of Medicine report (2) found that “An average of about 17 years is required for new knowledge generated by randomized controlled trials to be incorporated into practice, and even then application is highly uneven.” We are faced with the opportunity and responsibility of making proven products of the Human Genome Project readily available to those in need. From gene tests for highly penetrant Mendelian disorders to predictive tests for common complex diseases or prognostic tests for people already afflicted with diseases such as cancer genetic informa-

Fig. 2. Interacting components of genomics in health care. Benefits of genetics and genomics in the health care system are dependent on three interacting components.

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tion-based products and practice changes will emerge in the near future and for decades to come. Although it is tempting to focus on and take satisfaction in the possibilities that lie ahead, it is incumbent upon us all to develop policies and practices that ensure safety and efficacy first. We are embarking on a voyage of great promise and discovery, and to do so without adequate provisions would be unwise. We hope that by bringing together various constituencies, we can more ensure a safer and more rewarding journey, which by most accounts has no final destination beyond our common humanity and a desire to ease suffering.

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