Special article

Policy perspectives on the emerging pathways of personalized medicine

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Remarkable advances in the fundamental knowledge about the biological basis of disease and technical advances in methods to assess genomic information have led the health care system to the threshold of personalized medicine. It is now feasible to consider strategic application of genomic information to guide patient management by being predictive, preemptive, and preventive, and enabling patient participation in medical decisions. Early evidence of this transition has some hallmarks of disruptive innovation to existing health care practices. Presented here is an examination of the changes underway to enable this new concept in health care in the United States, to improve precision and quality of care through innovations aimed at individualized approaches to medical decision making. A broad range of public policy positions will need to be considered for the health care delivery enterprise to accommodate the promise of this new science and technology for the benefit of patients.

Dialogues Clin Neurosci. 2009;11:377-387.

Keywords: *personalized medicine; genome-wide association study; pharmacogenomics; health information technology; clinical decision support; in vitro diagnostic multivariate index assay; coverage with evidence development*

Simply stated, for personalized medicine to become a hallmark of mainstream modern medicine, the attributes of precision and meaningful improvement in quality of health care through technology and information management must be obvious and unequivocal. Throughout biomedical science, there has been much anticipation of the potential impact of genomic, molecular, and personalized medicine for health. The beginning of 21st-century biomedical research was heralded by the completion of the Human Genome Project, which gave a great deal of momentum to new capabilities of science and technology in the hands of medical practitioners and the public.

Across the spectrum of clinical neurosciences, many advances are clearly being made toward understanding the biological underpinning of disease. Applications of new technology platforms in research are widely seen in neurodegenerative disorders, neuropsychiatric conditions, addiction, and developmental disorders. While the impact of translation of these new research frontiers will likely take many years to be measured, pressing implications requiring important policy considerations are visible today.

Significant innovation and technological achievements lie at the heart of the rapid pace of accrual of scientific information to support personalized medicine. Dramatic decreases in cost and increases in analytical throughput have placed within reach the possibility of sequencing a

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person's entire genome for $1000. Broad applications of genomic characterization of disease states in the pharmaceutical, biotechnology, and diagnostic research sectors have become mainstays of early- and late-stage therapeutic development. Despite the robust investments in discovery research technologies to exploit genomic variation of disease-related genes, personalized approaches to disease management have raised challenges for industry because of the potential segmentation effect on diminishing the potential marketable population for new medical products. Nevertheless, there remains strong interest among pharmaceutical and biotechnology developers for clinical strategies to employ diagnostic tests in combination with therapeutic interventions. Whether this "codevelopment" approach will be widely employed by industry to enhance clinical development strategies, or is engaged in the clinical practice regimen as a personalized medicine tool, is largely unknown. The pathway toward large-scale use of molecular diagnostics in managing therapy decisions has substantial obstacles and misaligned incentives that will require significant policy modifications before personalized medicine becomes commonplace in health care.[1]
While today's view of the horizon for many aspects of clinical practice remains unclear, some disciplines of medicine, such as oncology, are rapidly adopting clinical genomic analysis and individualization of therapies. Some of the more relevant challenges are not the scientific validity of the use of genomic tools, but rather the capability to deploy and organize information in meaningful ways in clinical practice. In addition, it is important to recognize that all of the discovery research and technological advancement is occurring in a highly volatile climate of change in health care policy. Access to health care, public financing of health care services, moving away from fee-for-service reimbursement models, comparative effectiveness research, changing focus on preventive health services, looming financing challenges accompanying dramatic shifts in demographics of aging populations, and continued concerns regarding security and privacy of health information are all part of today's policy framework, representing a cauldron of change in health care.
In this overview, the policy perspective of the translation of genomic science into health care practice is examined under the moniker of personalized medicine. The focus through this lens addresses how advances in science, technology, and health care in the United States come together while recognizing that global influences in all of these domains are increasingly relevant to the domestic picture. Currently, personalized medicine addresses two general advanced technology platforms; molecularly targeted therapeutics which are selective for a specific biological marker (biomarker—defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[2]), and molecular diagnostics. The latter, relative to the neuroscience areas, can generally be considered to include genomic diagnostic tests, biobehavioral testing measures, and imaging technologies. While recognizing the value of the contribution of many advanced imaging technologies to drug discovery and development and clinical disease state assessment, this report is principally focused on genomic diagnostic technologies. Currently, three broad medical applications of these technologies are most frequently considered as personalized medicine approaches: to determine likelihood of clinical response with molecularly targeted agents, to determine polymorphisms likely to contribute to adverse events or subtherapeutic response to drugs, and to assess disease biomarkers as predeterminants for diseases and conditions, such as heart disease, neurodegenerative disorders, and cancer.
In 2006, the US Department of Health and Human Services (HHS) initiated a federal effort to coordinate and facilitate steps across the agencies to establish pathways to enable genomic and personalized medicine to enter health care. In recognizing potential obstacles that predictive, preventive, and pre-emptive approaches to health care may face, the Personalized Health Care Initiative was launched to avoid unnecessary delays and develop effective communication strategies for the intended use of these technologies in health care. The framework for this initiative was built on two fundamental tenets: that linkage of clinical and genomic information would yield insights into human health and disease, and that the information gained from this linkage would be used, and not misused, to benefit patients and consumers.[3] Recently, HHS published a report that included an analysis of health systems changes that were being undertaken in various institutions and through collaborative projects.[4] The report also looked at the need for changing roles of key stakeholders in successful transformation of services in health care, required to successfully implement personalized medicine practices.

These analyses featured some of the implementation issues associated with personalized medical care and some of the solutions to overcome them.

Definitions and context of personalized medicine

The use of the term "personalized medicine" in the literature predates the advances in clinical genomics that have advanced the biological understanding of differences between individuals. Applications of this terminology were often related to customized behavioral approaches to management of health conditions. Prior to the 1990s, the use of the term "personalized medicine" was used to imply that there were sociological, educational, and psychological bases for alternative approaches to patient management that led to more or less successful practices. In the late 1990s, somewhat simultaneously with the approaching completion of the Human Genome Project, more common usage of the term reflected genetic understanding for differences in pharmacotherapy, ie, pharmacogenomics. This also coincided with the market entry of several molecularly targeted therapies in oncology that used genetically based determinants for the development and subsequent clinical application of novel therapeutic agents. Trastuzumab (Herceptin®), a monoclonal antibody that serves as a treatment for breast cancer, has often been heralded as the first molecular therapy ascribed to personalized medical applications through the use of an assay to detect overexpression of the Her2 protein, thereby identifying patients who are most likely to respond.

Since then, there have been many interpretations and contexts applied to the term "personalized medicine." For the purposes of this discussion, the definition used here will be based on one by Willard et al as "the delivery of health care in a manner that is informed by each person's unique clinical information; genetic, genomic, and other molecular biological characteristics; and environmental influences. The goals of personalized medicine are to take advantage of a molecular understanding of disease, combined with other individual factors, to optimize preventive health care strategies while people are still well or at the earliest stages of disease."[5]

Increasingly, consumer interactions with the health care system and engagement in proactive participation in agenda setting and decision making are being applied to new ends. The rise of advocacy organizations and their involvement in therapeutic development, application of social networking enterprises for patient connectivity (ie, PatientsLikeMe), greater involvement of public members in policy development, and growing public influences on coverage and reimbursement policies add new context to patient advocacy. Greater public awareness and growing understanding of personal utilities afforded by information technology, genomic analysis-assisted disease risk assessment, and computer-assisted living devices all bring a broader context to this discussion, which is referred to here as personalized health care (as distinguished from medical context of diagnosis and interventions).[6]

While much of the emphasis in discussions about personalized medicine has been focused on medical technologies, aspects of information technology are becoming their equal in enabling individualization or mass customization of health care schemes. This is not unlike the disruptive innovation qualities that computers have had in other industries, and will likely lead to wide-ranging and equally disruptive change for the medical community.[7] One key characteristic of change will be the blurring of the lines between the established medical community, the patient/consumer, and other community members "linked" by information systems. In the future, personalized health care will represent an amalgam of patient experiences that will be customized, interactive, less episodic in nature, and more of a continuum of care. There will be many challenges ahead, in order for this model to be accepted and demonstrated to provide a higher quality of care, greater understanding by patients of their condition and health care choices, and improved efficiency and effectiveness of health care practices.

Key catalysts on the pathways to personalized medicine

The pace at which discovery research in human genomics enters translational research may be a trajectory unlike past novel interventions. In looking at personalized medicine through the lens of clinically meaningful impact, it is worthwhile to provide a context for some of the forces at play in creating the foundation for personalized medicine.

Genomic sequencing and related analytic platform technologies

The establishment of the public domain as the key reference source for the Human Genome Project opened the

door to discovery research that continues to pay dividends in advancing scientific frontiers. Additionally, the substantial investments in large-scale science included funding for technology platforms and their applications in the project itself. As a consequence, there was a surge in the development of sequencing technologies yielding remarkably higher throughput, dramatically reduced costs, and greatly enhanced analytic capabilities. Government-supported incentives for technology development created an economically feasible environment that has expanded genome-scale research capabilities from large sequencing centers to the laboratory bench, and now, virtual discovery research through computational analysis. These efforts were first engaged to sequence targeted regions of the genome, in order to understand polymorphisms in genes and their contribution to genetic disorders. The HapMap project, by building a widely diverse international public genome database, rapidly accelerated the capability to compare population-based genetic makeup, resulting in highly annotated databases of disease genes.[8] Evolutionary aspects of genomic information for understanding biological diversity came in the form of sequencing projects of other species. These projects yielded tremendous public resources that enabled biological understanding to be gained in model organisms, leading to broader insights into human development and disease mechanisms.

Advances in genomic information were not based solely on high-throughput sequence analysis. The development of microarray technology enabled ease of use for performing hybridization analysis on virtually any laptop computer. A new basis for diagnostic tests has been provided by the vast amount of gene expression data now available through large-scale measurement of mRNA abundance. The platform greatly expanded the capabilities to include comparative analysis of specimens for gene expression and the volume of genomic data that could be generated in hours of experimental time. Coupled with the development of analytical software, scientists are now armed with an adaptable platform to evaluate polymorphisms, compare the effects of interventions on DNA analysis, and ultimately evaluate pharmacologic impact on gene expression. Over the past 5 years, gene expression profiling has become a commonly used quantitative method in molecular and systems biology. In a short period of time, this technique has also become a common translational research tool widely applied in clinical medical laboratories, particularly in oncology for assessment of tumor biomarkers.

Genomic analysis platforms have had dramatic impact on clinical research and therapeutic research and development, and spawned a broad range of molecular diagnostic assays and devices. Meanwhile, medical applications remain unclear, as the clinical experience and evidence is lacking for many potential uses. Pharmacogenomics is viewed by many as a discipline of clinical pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. By doing so, pharmacogenomics provides a rational means to optimize drug therapy with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects. This approach sets the stage for personalized medicine, in which drugs and drug combinations are optimized for each individual's unique genetic makeup. The clinical impact of this has been primarily recognized in the alteration of many drugs' biotransformation profiles as a result of polymorphisms that contribute to slow or rapid metabolism. These manifestations are relevant to a broad range of pharmaceuticals, leading to either subtherapeutic responses in the case of enhanced activity of drug metabolizing enzymes, or adverse events from toxicologic manifestations of slowed drug inactivation. These studies have led to implications by the US Food and Drug Administration (FDA) to notify prescribing clinicians that pharmacogenomic testing may be of value in dosing and therapeutic selection, in some cases. The FDA maintains a list of drugs with labeling requirements that under some circumstances require pharmacogenomic testing of subpopulations for polymorphisms before the drug is prescribed.[9,10]

Analysis of pharmacogenomic data has become a substantial undertaking by the FDA. Among these steps in developing the translational science for the future, the FDA, together with the pharmaceutical industry and academic investigators, has established a voluntary data submission process to enable better understanding of the interaction of developmental therapies with genes and their clinical manifestations.[11] Arguably, the largest number of patients with potential clinical application of a pharmacogenetics test under consideration in medical practice today are those who will be prescribed the anticoagulant warfarin. Several polymorphisms lead to the abnormal metabolism of the drug, which has a narrow therapuetic index fraught with medical complications. Research continues on the clinical importance of routine

testing of the *Cytochrome P450 2C9* locus, which is involved in warfarin metabolism, and variants in *Vitamin K epoxide reductase* (*VKORC1*). Several commonly used drugs for neurologic conditions have FDA labeling for pharmacogenomic implications. Carbamazepine-related Stevens Johnson syndrome has been linked to polymorphisms in the *HLA B* haplotype. Individuals carrying one or two *1502 alleles are advised to avoid carbamazepine. Labeling for pharmacogenetic assay consideration is also present for fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) metabolized by *Cytochrome P450 2D6.* Abnormal clinical response may occur due to aberrant drug metabolism, and genetic testing may yield useful information to aid in dosing parameters.[12] A commercially available microarray has been developed and FDA approved for use to assist in determining *Cytochrome P450* polymorphisms, and other clinical laboratory tests are used in a variety of settings for consideration in drug dosing.[13]

Nonpolymorphic genetic modifications are increasingly being applied to understand gene-environment interactions in diseases and clinical conditions. Further expansion of the capabilities of microarray technology has enabled genomic analysis at additional levels by measuring DNA methylation and histone modification.[14] In addition, analysis of copy number is providing insight about genomic variation beyond nucleotide polymorphism, showing significance in the etiology of cancer, atherosclerotic heart disease, and complex neurological conditions such as Alzheimer's disease and schizophrenia.[15,16] Although not as commonly applied in the clinical laboratory as expression profiling, these methods are showing promise in therapeutic research and development and translational research genomic analytical laboratories.

Clinically meaningful laboratory applications in the future will need to overcome significant barriers. Currently, there are not widely accepted methods and standards for performing genomic analysis using array platforms. There is also wide variation in the analytical and computational methods used in comparative genomic analysis. In addition, there is a paucity of standardized control biomaterials for use in analyses. Finally, all of these quantitative measures are highly sensitive to clinical specimen acquisition, preparation, and storage methods. Little comparative work on standards for controls and disease biospecimens has been done on establishing normal datasets for gene expression methods. Recently, a summary of these issues was addressed through a guidance document issued by the Centers for Disease Control and Prevention (CDC).[17] The lack of highly annotated and fully characterized biospecimens with longitudinal phenotypic and demographic information remains a significant barrier for all of translational research in personalized medicine, but is most notable in large-scale genomic analyses.[18]

The application of the various genomic technology platforms has led to transformative research in population genetics. Over the last several years, population-based research studies, such as the Framingham Heart Study, have enabled large-scale genomic analyses from clinical resources. Collectively, these genome-wide association studies (GWAS), have enabled cross-study analyses from publicly available databases known as dbGAP (database of genotype and phenotype).[19] Over the past several years, hundreds of new GWAS results have yielded insights into multigene effects to a wide variety of human diseases and conditions. Many of these new mutations are identified in noncoding regions. Collectively, the discovery of these new associations is prompting more hypothesis generation about disease pathways than generating platforms for new diagnostics and therapeutics. These public resources are proving to be useful discovery resources for various disease areas, such as psychiatry, enabling consortia of investigators to use statistical analytic methods to map genetic architecture of common disorders.[20]

Information technologies in health care and impact on personalized medicine

A key infrastructure needed to establish a medical practice environment for individualized decision making is a robust and facile information technology capability. The reasons for this are the dependency on key attributes about the patient's health status, detailed data needs for phenotypic characteristics, and the complexity of the types of analytical data and decision algorithms that will be used to support more precise, preferred, and predictive health outcomes for the patient.

Much of the advances in genomic research have been supported by computational studies that have enabled large databases to be assembled with highly contextualized data to develop associative information about the relation of genes and biology. While technological advances in capacity for sequencing analysis have

exceeded the benchmark measure of computing power, Moore's Law, there is no doubt that this success has been largely tied to computational advances.

The transfer of this knowledge from the laboratory to the health care setting faces a steep climb to establish information management practices in the US. Improved clinical knowledge from research is highly dependent on recovering standardized, useful clinical information from medical practice. The delivery of knowledge in clinically useful formats to support decision-making processes is similarly critical. The information management needs to span these gaps is found in the electronic health information technology (health IT). The major components of a health IT system to support personalized medicine includes widely used electronic medical record systems and personal health records that consumers can use for recording their own health care information. A second component is a nationwide effort to enable health information exchange among health care providers and institutions that will enable portability of information to suit purposes on demand. A third element includes electronic decision support capabilities that engage medical records systems to facilitate evidence-based health care choices by the health care provider. Collectively, these are dependent on data standards that enable semantic and syntactic interoperability of data across health IT systems. As a health care enterprise, the US has a dearth of electronic information to support these needs, and it will take many years to achieve all of these steps to benefit all patients. The inability to connect information sources is a major contributor to the high costs of clinical research, particularly clinical trials. Despite escalating health care costs and substantial service inefficiencies in the US, there has been little incentive until recently to make capital investments in information systems for the inpatient and ambulatory care setting.

Today, less than 20% of all physicians use electronic health record systems, and far fewer have systems that provide decision support capabilities to aid personalized medicine. Some progress is being made on the requirement for electronic transmission of prescriptions from the health care provider to the pharmacy. Computerized physician order entry (CPOE) for ordering laboratory tests and other services has also been improving. As part of the American Recovery and Reinvestment Act of 2009, nearly $20 billion will be invested in the next several years to build health IT capacity through network capabilities, support acquisition of electronic systems by practice groups and health care institutions, and provide fiscal incentives for adoption and use of health IT systems.[21]

The ability to harness clinical information and use it for research applications will be crucial for personalized medicine to benefit from these national investments. Paramount for patients is the knowledge that their information will be handled securely, that their privacy in health matters will be protected, and that the confidentiality of this information is respected. Altogether, for personalized medical practice to flourish and provide meaningful value, a health information exchange system must be developed that enables information to be mobile, standards-based, and support evidence-based medical care practices. The yield from this will be greater use of health care provider resources, more precision and predictability in medical choices, and provision of patients with more information and choices to address their needs.

Public databases and data access

One of the key facets enabling the rapid entry of genomic information into clinical application is the policy framework that underpinned the dissemination of research information. The public aspects of federally funded research did not stop with the completion of the human genome project. While the early part of this decade led to the birth of commercial entities that build genomic databases, the avenues of public information resources continued to evolve. A series of policies led major science and medical journals to require submission of newly discovered gene sequences into GenBank. This process of openness continued with establishment of additional databases requiring transparency of research, enabling resources to be used for new discovery rather than replication of results. One of the key building blocks for establishing the base for personalized medicine and the rapid advances of genomic research was built on fundamental public access policies initiated in the 1990s. In 1996, free Internet access to the National Library of Medicine Medline holdings of scientific information rapidly accelerated the dissemination of new science. The National Center for Biological Information added immense public databases of genomic information, imaging repositories, and many other resources that support the translation of research into medical applications. Further advancing this is a policy implemented in 2008

requiring all NIH-funded scientific publications to be made publicly available within 12 months of publication.[22] PubMed Central, an open-source digital information resource, was established in February 2000 and has been followed by additional open-source publication venues. The net yield of these public policy efforts was to make biological information more readily available and accelerate the application of discovery research into clinical and translational research. While it is difficult to quantify the impact of public policies on the openness of scientific information, the effects have been widespread. Lowering barriers to commercial sector technology development, increasing the diversity of scientific collaborations, and enabling global research collaborations through the open language of science have been important steps to accelerate the arrival of personalized medicine.

Taken together, the profound advances in informatics platforms, allowing large and complex data to be moved rapidly, coupled with computational capabilities for gleaning meaningful associations of biological systems, have been transformative. Policies promoting sharing and dissemination of information have had a similar impact on accelerating the pace of science.

Vocabulary standards

The Human Genome Project brought with it a key aspect of data standards guiding the vocabularies of genetic information. The requirement to use internationally accepted common data elements for gene nomenclature and reference sequence information has provided specificity and avoided (to a large degree) confusion about the meaning of scientific data. Structuring digital biology to conform to unified modeling language (UML) has enabled genomic information to be modeled across all domains of scientific application through genomic standards, which has aided in the translation to clinical application. Standard clinical nomenclature is now being widely accepted for genomic test information. Health Level 7 (HL7), Online Mendelian Inheritance in Man (OMIM), Logical Observation Identifiers Names and Codes (LOINC), and Systematized Nomenclature of Medicine (SNOMED) provide widely accepted standards for clinical definitions, including disease and condition terminology, laboratory test information, and other terms for health care practices. Highly annotated clinical reference repositories for standards have been developed including the National Cancer Institute repository of data elements caDSR (cancer data standards registry and repository). The caDSR is a database and a set of Application Programming Interfaces (APIs) and tools used to create, edit, control, deploy, and find common data elements (CDEs) for metadata consumers and for UML model development.[23]

Protection of civil rights regarding genetic information

On May 21, 2008, the US framework of civil rights was enhanced through the signing into law of the Genetic Information Non-discrimination Act of 2008 (GINA).[24] This legislation was long sought on behalf of public interest, as the absence of federal regulations to prohibit use of genetic test information in employment decisions and provision of health insurance benefits on the basis of inherited traits was a deterrent for individuals to participate in research studies. Together with the Health Insurance Portability and Accountability Act provisions (HIPAA), GINA generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or an individual's family for decisions regarding coverage, rates, or preexisting conditions. The law also prohibits employers from using genetic information for hiring, firing, or promotion decisions, and for any decision regarding terms of employment. Importantly, the statute provides definitions regarding the consideration of genetic test and its application under GINA.

Regulatory oversight of genetic testing

In the US, the proliferation of genetic tests has raised awareness about a dichotomy in the regulatory framework across technology platforms and the federal agencies that oversee them. Molecular diagnostics that are performed in a laboratory as a laboratory-developed test are overseen by federal regulations issued under the Clinical Laboratory Improvement Act of 1972 (CLIA) that addresses the analytical validity of the testing procedures. Analytical validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. Examples of common tests of this type include cytogenetic studies, immunohistochemical analyses, and fluorescent in situ hybridization assays performed by clinical reference laboratories.

Molecular laboratory assays that are assembled and marketed as "kits" are medical products reviewed by the

FDA for analytical validity and clinical validity. Clinical validity of a genetic test defines its ability to detect or predict the associated disorder or phenotypic presentation. In this scenario, kits such as the polymerase chain reaction assay can be used in a clinical setting that may be outside of the clinical reference laboratory. The FDA review of these assay kits is considered a medical product under regulations of devices. In recent years, there has been much discussion regarding the different pathways that genomic assays may be brought into the clinical market based on the oversight of laboratory tests. Much of this discussion has been centered on a subset of clinical tests known as in vitro diagnostic multivariate index assays (IVDMIA) that integrate the analysis of multiple genes on technology platforms, providing an index score as a result. The mathematical algorithms that reflect the integration of these various gene expressions or polymorphisms are based on clinical population studies that associate the interaction of various genes under different clinical scenarios. Today, IVDMIA are used in guiding treatment decisions in breast and colon cancer, and providing clinical guidance regarding likelihood of recurrence under various treatment regimens. These tests are performed in clinical reference laboratories and are not subject to FDA review. A draft guidance has been issued that proposes that manufacturers of IVDMIA obtain premarket approval. Recognizing that the potential for a large number of complex genetic tests will be coming into the clinical marketplace in the near future, the Secretary of Health and Human Services requested a review of the federal oversight of genetic tests. The Secretary's Advisory Committee on Genetics, Health, and Society issued a comprehensive report in April 2008 that highlighted the impediments to data supporting medical use of genetic tests and recommended steps to improve the oversight process.[25]

Policy issues regarding clinical utility and medical benefit from the use of genetic tests

Beyond the regulatory review of medical products, the integration of personalized medicine technologies into clinical practice also requires coverage and reimbursement of costs of the tests by health care insurance providers and other organizations that pay for health care services. A centerpiece of these considerations is the evidence that supports genetic test information adding value to the medical care experience. The clinical utility of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. Overall, the framework for supporting coverage and reimbursement decisions for genetic tests has been hampered by the lack of substantive clinical data to demonstrate confirmed value for their use in health care. The lack of a clinical trial infrastructure for diagnostic assays, similar to that for drugs and biologics, has made demonstration of clinical utility and medical effectiveness difficult to demonstrate. For personalized medicine applications, economic issues play some part in the inability of small diagnostic companies or reference laboratories to perform randomized clinical trials to show benefit by the determination of medical intervention on the basis of treatment outcome.

One suggested framework for considering the composite evidentiary needs for genomic tests identifies important information needs for medical use.[26,27] In 2004, the Centers for Disease Control and Prevention (CDC) initiated a program to systematically review the clinical evidence supporting applications of genetic tests. The program, known as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) conducts systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in the transition from research to clinical and public health practice.[28] Through this program, CDC supports evidence evaluations through literature reviews. One of the first studies conducted involved the use of pharmacogenetic testing of *Cytochrome P450* polymorphisms in patients being prescribed SSRIs. The evidence review concluded, as it has for a variety of other genetic tests, that there was insufficient data to support routine use of genetic testing.[29] Multiple other studies have been conducted to examine other genetic tests and similar findings were noted. This pattern suggests that to fully integrate genetic testing practices into health care, substantially more clinical research is needed to demonstrate clinical utility.

Health care financing considerations about coverage and reimbursement of genomic tests

The Centers for Medicare and Medicaid Services (CMS) recently deliberated on the coverage and reimbursement of pharmacogenomic testing. Coverage decisions regarding new health technologies under Medicare can be han-

dled in two ways: local coverage decisions that are made by petitioning authorization by the sponsor to a regional Medicare contractor, or a national coverage decision that CMS itself coordinates through administrative processes. The latter was employed by CMS recently through the conduct of an evidence review for coverage consideration of pharmacogenomic testing of genes associated with the biotransformation of warfarin, a powerful anticoagulant. In May 2009, after extensive review, CMS made a decision that denied coverage for routine warfarin pharmacogenomic testing as their findings indicated that clinical utility had not been demonstrated. CMS went further to outline parameters for future studies that they would consider supporting under a "coverage with evidence development" process. This process allows for the reimbursement of tests if done as part of a randomized clinical trial where utility can be assessed. To date, the alignment of evidence needs for pharmacogenomic tests to meet clinical validity and utility have not been mapped sufficiently for clinical studies to meet the regulatory needs of FDA and CMS. Further work in advancing the application of pharmacogenomics in medical practice could benefit from most strategic alignment of evidence needs and resources to support these studies.

The perspective of personal utility of genomic information has opened a door for new business opportunities in consumer health services. In 2008, several new direct-to-consumer services were launched, providing relatively low-cost genomic analysis and interpretation capabilities to the public, without a physician order. 23andMe, Knome, deCODEme and Navigenics are among the companies offer comprehensive genomic analysis and interpretation to consumers via a Web-based linkage. These services provide health information to patients about various personal traits (including behavioral tendencies) and risk assessment probabilities. The genomic tests in these cases are performed in CLIA-certified laboratories but not FDA approved. Some controversy has arisen over the validity of these tests and the consistency of analysis across platforms and databases. Furthermore, there is concern that none of the genomic information provided is directly medically actionable. Other genetic testing services focused on specific genetic mutations and their associations to neurologic and psychiatric conditions using data developed from GWAS studies have arisen, including those predicting likelihood of autism spectrum disorders, and suicidal ideation related to SSRIs. Due to the lack of substantive clinical trials showing evidence to support these claims and the potential to cause patient confusion about the interpretation of the results, these tests have largely been controversial.[30] Among the issues frequently mentioned about the consumer genomics services are the variation in reference data populations used by the different services accounting for different interpretations of risk for the same patient, oversight of the clinical laboratory measurements through CLIA, and transparency of the use of the consumer information by the service providers.

Federal Trade Commission authorities are also playing a role in assessing unscrupulous marketing tactics by some companies of tests with unsubstantiated claims of benefit. Despite the uncertainty, these trends indicate several factors. Some segments of the consumer base are interested in potential genetic risks and may use this information to guide lifestyle and behaviors in their own health care. Moreover, the interest in consumer genomic services demonstrates some level of consumer empowerment and self-determinism that now permeates other segments of health care through social networking and community engagement. How these early experiences in commercial sector genomic services relate to future applications is unclear. The likelihood is, however, that armed with risk information, consumers will seek more insights from health care providers to guide them in the use of this information. Most health care providers, however, are poorly equipped at the present time and access to medical genetic counselors is sparse, although provided by some of the current consumer services.

Conclusions

Overall, the impact of genomic technologies on the understanding of disease and environment interactions has been substantial. To translate these advances into health care as personalized medicine will require substantial innovation in a systems redesign yielding transformative changes in the values, priorities, and roles of all participants. Building on information policies in research, we can anticipate that personalized medicine, in the context of health care reform, will need to address some key areas. Molecular diagnostics, for example, are likely to be required to have higher levels of transparency of supporting data, and confirmatory evidence that meaningful therapeutic selection decisions can be made on the basis of the information they provide. Some

important decisions will need to be addressed in establishing a clinical research framework for evidence development in testing the applications of molecular diagnostics. Achieving this will almost certainly require more collaborative interactions between public and private sectors.

The attributes of potential cost savings through the reduction of adverse events and avoidance of using therapeutics when patients will experience no benefit will need substantive clinical evidence to support coverage and reimbursement policies. Application of genomic analysis in risk determination and behavioral and preventive interventions requires substantially more research to achieve the most beneficial applications of scare resources. Furthermore, there will likely be a greater role for government-sponsored or public-private collaborations to support prospective and comparative trials to evaluate the contributions of genomic-based diagnostic tests. Improvements in cost accounting throughout health care will be required to demonstrate the evidence that supports early detection and prevention strategies yield relevant health outcome benefits. Efforts to identify key data needs to assess clinical utility and cost-effectiveness of molecular diagnostics overall will help refine innovation goals for clinical application of genomics, and provide innovators with more specific targets for their research and development investments. Finally, substantial needs exist for education and training of health care providers across many disciplines to understand the patient care objectives of personalized medicine. If the course of these developments is focused on patient care and quality improvement processes, the future contributions of personalized medicine to patient care will be substantial. ❑

Acknowledgements: Jessica Nadler, PhD and Constanze Coon, PhD contributed to manuscript preparation and editing.

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Perspectivas estratégicas en los nacientes caminos de la medicina personalizada

Los notables avances en el conocimiento fundamental acerca de las bases biológicas de la enfermedad y los avances técnicos en los métodos para evaluar la información genómica han conducido al sistema de asistencia sanitaria a las puertas de la medicina personalizada. Ahora es posible considerar la aplicación estratégica de la información genómica para que el manejo del paciente resulte predecible, prioritario y preventivo, y se permita la participación del paciente en las decisiones médicas. La evidencia inicial de esta transición tiene algunas características particulares en cuanto a que las innovaciones alteran las prácticas de la asistencia sanitaria existentes. Se presenta una evaluación de las modificaciones que están en proceso para permitir que este nuevo concepto de atención sanitaria en los Estados Unidos aumente la precisión y la calidad de la atención a través de innovaciones dirigidas a propuestas individualizadas para la toma de decisiones médicas. Será necesario considerar una amplia gama de posturas de políticas públicas para las empresas prestadoras de atención sanitaria para que ajusten las promesas de esta nueva ciencia y tecnología para el beneficio de los pacientes.

Perspectives stratégiques dans la voie de la médecine personnalisée

Des avancées notables dans les connaissances fondamentales des bases biologiques des maladies et des progrès techniques dans les méthodes d'évaluation de l'information génomique ont permis de faire évoluer le système de santé au seuil de la médecine personnalisée. Il est désormais possible d'utiliser des applications stratégiques de l'information génomique pour guider la prise en charge du patient, afin qu'elle soit prédictive, préemptive, et préventive, et qu'elle permette la participation de celui-ci aux décisions médicales. Cette transition s'est illustrée de manière précoce par des innovations qui tranchaient avec les pratiques soignantes existantes. Nous examinons ici les modifications nécessaires à l'émergence de ce nouveau concept de soins aux États-Unis afin d'améliorer la précision et la qualité des soins par des innovations visant à individualiser la prise de décision médicale. Adapter cette nouvelle science prometteuse et la technologie pour le bien des patients nécessitera d'envisager une grande variété de positions dans l'élaboration de la politique des pouvoirs publics au service de la santé.

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