REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-10)
Genomic-based Personalized Medicine
(Reference Committee E)

EXECUTIVE SUMMARY

Objectives. The term "personalized medicine" (PM) refers to health care that is informed by each person's unique clinical, genetic, and environmental information. Clinical integration of PM technologies is enabling health care providers to more easily detect individual differences in susceptibility to particular diseases or in response to specific treatments, then tailor preventive and therapeutic interventions to maximize benefit and minimize harm. This report will review current status of genomic-based PM and challenges to implementing it, and will briefly summarize the activities of key federal agencies, professional organizations, coalitions, and health systems that are working to further the integration of genomic-based technologies into routine care.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 2005 and 2010 using the search terms "personalized medicine" and "personalized medicine AND clinic." To capture reports that may not have been indexed on PubMed, a Google search was also conducted using the search term "personalized medicine." Additional articles were identified by review of the literature citations in articles and identified from the PubMed and Google searches.

Results. Genetic testing has been a routine part of clinical care for a number of years in screening and diagnosis. Recently, a number of genomic-based applications have advanced beyond these screening and diagnostic techniques and are "personalizing" the delivery of care by enabling risk prediction, therapy, and prognosis that is tailored to individual patients. Yet there are challenges to the clinical implementation of PM, such as the lack of genetics knowledge among health care providers, slow generation of clinical validity and utility evidence, a fragmentary oversight and regulatory system, and lack of insurance coverage of PM technologies. A number of programs and activities at both the federal and private levels are focused on overcoming the challenges and facilitating appropriate clinical implementation of PM by conducting research, providing education and resources, and evaluating the quality of genomic applications.

Conclusions. PM promises to enable the tailoring of treatments and preventions for individual patients. In order to maximize the benefit of PM technologies for patient care, several barriers need to be addressed. Most importantly, the health care workforce must become educated about the clinical use of genetic technologies. Also, better systems of oversight and regulation must be implemented, an exploration of the type of evidence that is sufficient to demonstrate clinical validity and utility should be undertaken, and coverage of clinically useful PM applications should be considered by insurers. Our American Medical Association (AMA) recognizes the importance of genomic-based PM in the delivery of care and will continue to develop educational resources and point-of-care tools to assist in its clinical implementation. Our AMA also will continue to represent physicians' voices and interests in national policy discussions of issues pertaining to the clinical implementation of genomic-based PM.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4-A-10

Subject: Genomic-based Personalized Medicine

Presented by: C. Alvin Head, MD, Chair

Referred to: Reference Committee E
(Brooks F. Bock, MD, Chair)

At the 2006 Annual Meeting of the House of Delegates (HOD), Council on Science and Public Health Report 4, "Genomic- and Molecular-based Personalized Health Care," (AMA Policy D-460.976, AMA Policy Database) was presented to the HOD and its recommendations adopted.[1] The report reviewed the use of genetic information to enhance patient care and the potential implications of the human genome for research and development and clinical practice. It also briefly identified public policy issues surrounding the use of genomic information. The Council believes that genomic-based technologies are increasingly impacting the delivery of care, and therefore initiated the development of this report to serve as an update to its 2006 report

The term "personalized medicine" (PM) refers to health care that is informed by each person's unique clinical, genetic, and environmental information.[2] While the principle of providing care that is appropriate for each individual patient has always been the goal of physicians,[3] PM can be considered an extension of traditional approaches, enabling further refinement of diagnosis, treatment, and prevention.[4] PM is envisioned as generating a new model for health care that is based on proactive and preventive health planning, as opposed to a traditional reactive approach that often does not identify disease until it is already manifest and sometimes irreversible.[2] Forming the foundation of PM are genomic-based methods, such as genetically-informed risk prediction and therapeutic tools and evaluation of family health history; and health information technology (HIT) that includes electronic health records (EHR), clinical decision support (CDS), and health risk assessment algorithms.[2] Armed with the integration of these technologies, health care providers may more easily detect individual differences in susceptibility to particular diseases or in response to specific treatments, then tailor preventive and therapeutic interventions to maximize benefit and minimize harm.[4] Although HIT plays a vitally important role in PM, this report will focus on genomic-based technologies; it will review current status of genomic-based PM and challenges to implementing it and will briefly summarize the activities of key federal agencies, professional organizations, coalitions, and health systems that are working to further the integration of genomic-based technologies into routine care. (Acronyms used throughout the report are defined in Appendix I.)

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2005 and 2010 using the search terms "personalized medicine" and "personalized medicine AND clinic." To capture reports that may not have been indexed on PubMed, a Google search was also conducted using the search term "personalized medicine."

Additional articles were identified by review of the literature citations in articles and identified from the PubMed and Google searches.

GENOMIC-BASED PM APPLICATIONS

Genomic-based PM is rooted in the detection of genetic variations that cause disease or increase disease risk or susceptibility. Knowledge of the genetic basis of disease has grown rapidly during the last 20 years, revealing the mutations and variations that cause disease or are associated with an increase in disease risk. Concurrent with the growth in this knowledge, the technology that underlies genetic analysis has gotten more sophisticated, efficient, and less costly, making genetic testing more accurate, rapid, and affordable.[2,5] As a result, tests that detect genetic variations have proliferated. Close to 2,000 genetic tests are now available to health care providers, researchers, and consumers.[6] These tests are aimed at predicting disease risk and susceptibility, diagnosing disease, guiding therapeutic options, predicting prognosis, and in some cases, guiding lifestyle choices.

Genetic testing has been a routine part of clinical care for a number of years. For example, diagnosis of single gene disorders such as cystic fibrosis or Huntington's disease are guided by the results of genetic testing.[6] Much of newborn screening, designed to detect and provide treatment for disorders that, if left untreated, would lead to early mortality or severe lifelong disability, is genetically based.[7,8] Carrier screening, preimplantation genetic diagnosis, and prenatal diagnosis are valuable tools for calculating risk of passing on disease alleles to a future child, and detecting manifestation of genetic disease in an unborn child, respectively.[9-11] However, in recent years, a number of genomic-based applications have advanced beyond these screening and diagnostic techniques and are "personalizing" the delivery of care, i.e., enabling risk prediction, therapy, and prognosis that is tailored to individual patients. Used in combination with evaluation of familial inheritance patterns, PM applications have the potential to significantly improve patient care by ensuring that each patient is treated appropriately and effectively. Below are examples of the genomic-based PM applications that are being used to enhance the delivery of care.

Predicting Disease Susceptibility

Family Health History. Health care providers have long been using genetics to predict disease risk by collecting patients' family health history (FHH). A carefully collected FHH can show genetic inheritance patterns and often reveal who in the family may be at risk for certain diseases, thereby defining appropriate candidates for further evaluation, such as genetic screening or diagnostic testing, and who may be candidates for preventive strategies, such as lifestyle changes and early treatments.[2,12] FHHs are widely used by clinical geneticists, genetic counselors, and other health care professionals in risk assessment for single-gene disorders and hereditary cancer syndromes. Primary care physicians are often the first to encounter patients with possible genetic disorders; therefore, a FHH is an important tool in the primary care setting for informing referral and management decisions for a wide number of diseases. Several groups recommend that all health professionals understand the importance of a FHH.[13-15] Unfortunately, FHH collection competes with other clinical tasks for limited provider time;[16,17] primary care visits average less than 20 minutes,[18] with only approximately 2.5 minutes spent on discussions of FHH.[16] The U.S. Surgeon General encourages patients and families to collect their own FHH and share it with their physicians.[19] It is important for physicians to be aware that patients often lack awareness, understanding, and recollection of their FHH, and differing interpretations of the term "family" exist.[12,20]

Since the genetic basis of complex diseases such as diabetes and cardiovascular disease is becoming more clear, more study is needed to determine how best to use FHH to determine disease risk and inform patient management strategies. A 2009 evidence report by the Agency for Healthcare Research and Quality addressed issues relevant to the collection of FHH in the primary care setting,[21,22] and a recent National Institutes of Health (NIH) State-of-the-Science Conference called for studies that examine which key elements of a FHH should be used for the purposes of risk assessment for common diseases, whether the collection of FHH will improve health outcomes for the patient, and how accurate is the information collected from patients.[12]

Genetic Susceptibility Testing. Genetic tests are increasingly being used to personalize the prediction of disease risk or susceptibility. One of the most well-known examples of this type of test is BRACAnalysis®, which predicts the risk of developing hereditary breast and ovarian cancer by detecting mutations in the *BRCA1* and *BRCA2* genes.[23] Women who carry certain *BRCA* mutations have a 50-80% chance of developing breast cancer by age 70, and have elevated risk for ovarian and other cancers; men who carry *BRCA* mutations also are at elevated risk for developing breast and other types of cancer, such as prostate, pancreatic, and colon.[24] While only a small number of breast cancer cases are caused by *BRCA* mutations, the test is often performed when FHH and the patient's own health history reveal *BRCA*-associated cancers. Positive, negative and uncertain test results have important implications for future cancer risk, screening, preventive therapy, and risk in family members. Family members also may choose to be tested so that they too can make informed decisions about preventive options.

Notably, BRACAnalysis® has been the subject of a recent patent dispute. Myriad Genetics, the developer and manufacturer of the test, together with the University of Utah, holds patents on the *BRCA* genes; Myriad is the sole provider of full-sequence *BRCA* testing in the U.S. and has licensed only a few other laboratories to perform other *BRCA* diagnostic testing. In 2009, the American Civil Liberties Union represented several medical professional organizations, including the AMA, in a suit against Myriad, arguing that the patents have had a chilling effect on technological advancements and patient access to *BRCA* diagnostic testing.[25] In March 2010, a U.S. District Court invalidated the patents, but Myriad has stated that it will appeal the ruling.[26]

Several other genetic tests exist that predict susceptibility to disease. For example, individuals with a strong FHH of colorectal and/or endometrial cancer can be tested for mutations in the genes *MLH1*, *MSH2*, *MSH6*, and others, which are characteristic of hereditary colorectal cancer syndromes.[27] Those who carry mutations in these genes have a risk as high as 60-80% for developing colorectal and endometrial cancers.[28] A positive result indicates the need for earlier and more frequent colonoscopy screening, with the goal of earlier detection. A number of gene variations associated with an increased risk for both early-and late-onset Alzheimer's disease can be detected by genetic testing.[29] Genetic tests also are available to predict risk for developing age-related macular degeneration.[6]

It is important to note that some genetic tests (especially those that predict risk of developing a complex disease caused by a combination of genetic variations and environmental components) have unproven clinical utility; clinical utility represents the ability of a test to improve health outcomes.[30] With proper evidence generation, these genetic tools could be promising resources for personalized screening and prevention.

Predicting Prognosis

Genomic profiling of tumor tissue has been widely used to inform the diagnosis and management of cancers. More recently, genetic tests are being used to predict survival and benefit of chemotherapy for those diagnosed with breast cancer. For example, MammaPrint® and Oncotype DX® are designed to predict the risk of developing distant metastases in women of a certain age and breast tumor type.[31,32] Both tests analyze the expression of a series of tumor genes, and based on expression levels, predict chance of recurrence-free survival at 10 years. Oncotype DX® additionally predicts the magnitude of benefit from chemotherapy.[32] The clinical validity, (i.e., the ability of the test to predict its associated disorder) of MammaPrint® and Oncotype DX® has been established.[31] While retrospective studies have pointed to the clinical utility of the tests, clinical trials collecting evidence to more conclusively demonstrate it are underway.[33,34] The use of Oncotype DX® in addition to other elements of risk stratification to guide chemotherapy treatment decisions is now included in the recommendations of the National Comprehensive Cancer Network, the American Society of Clinical Oncology (ASCO), and the College of American Pathologists (CAP).[31,35-37]

Monitoring Surgical Outcome

Genetics is now being used as a tool to monitor risk for tissue rejection following transplantation. Endomyocardial biopsy has been the standard method for monitoring tissue rejection after cardiac transplantation; however, it is invasive, expensive, and subject to sampling error. Gene expression profiling of peripheral blood mononuclear cells (PBMC) has been shown to distinguish patients in post-transplant quiescence versus those in acute rejection.[38] Such tests (e.g., AlloMap®) examine the expression level of several genes in PBMCs of patients who have undergone cardiac transplantation, offering a non-invasive, accurate method of monitoring risk for tissue rejection.[2] A small trial recently showed that use of AlloMap® resulted in significantly fewer biopsies without increasing serious adverse outcomes.[39]

Informing Drug Therapy: Pharmacogenomics

One of the most well-studied facets of PM is pharmacogenomics, the study of inherited genetic variations that influence individual response to drugs. Disposition processes, such as drug absorption, distribution, metabolism, and excretion, determine the pharmacokinetic behavior of the drug in individual patients and the time course of the drug/plasma concentration profile. Genetic variations in genes that encode drug transporters, drug metabolism enzymes, and receptors are key factors in altering drug responses in some individuals. Knowing whether a patient carries these variations can often aid in individualizing drug therapy, and may decrease adverse drug reactions while increasing the effectiveness of drugs. Pharmacogenomics has been characterized as "getting the right dose of the right drug to the right patient at the right time."[40]

Among the most common genes responsible for differences in drug metabolism and response are the *cytochrome P450* (*CYP*) genes, encoding enzymes that control the metabolism of more than 70% of prescription drugs. People who carry variations in certain *CYP* genes often do not metabolize drugs normally. Other genes known to affect drug response encode the receptors for regulatory molecules such as hormones, cytokines, and growth factors, and cellular proteins such as enzymes, transporters, carriers, ion channels, structural proteins, and transcription factors. Variations in these genes can lead to altered responses and adverse drug reactions by disabling, inactivating, interfering with, or influencing the signaling mechanisms or cellular machinery that mediate the effects of the drug.

Pharmacogenomic testing, which detects variations in genes required for normal drug metabolism and response, can be used to avoid adverse drug reactions, predict effectiveness, and predict the

correct drug dose. The product labeling for more than 200 drugs now includes information about the influence of genetics on drug response or safety, and in some cases, recommends genetic testing.[4,40] A full table of drugs subject to pharmacogenomic variation can be found on the Food and Drug Administration's (FDA) Web site and on the Web site of the Indiana University Division of Clinical Pharmacology.[41,42] Below are examples of drugs for which genetic testing to determine pharmacogenomic effect may be beneficial.

Predicting Adverse Drug Events. Several drugs can cause severe and life-threatening reactions in patients with genetic variations in genes that metabolize or are targets of the drugs. Abacavir (marketed as Ziagen) is a nucleoside reverse transcriptase inhibitor used in combination with other antiretrovirals to treat HIV infection.[43] An immunologically-mediated hypersensitivity reaction occurs in 5-8% of patients taking abacavir. The hypersensitivity symptoms include a combination of fever, rash, gastrointestinal tract symptoms, and respiratory symptoms that become more severe with continued dosing.[44] This hypersensitivity is associated with a variant allele of the major histocompatibility complex, *HLA-B*5701*. Patients who carry the variant allele have an increased risk for developing a hypersensitivity reaction.[44] *HLA-B*5701* screening before abacavir treatment results in a significantly reduced number of hypersensitivity cases.[44] The abacavir product labeling recommends genetic testing before prescribing it.[43]

Other drugs that have the potential to cause serious adverse events in patients with certain genetic variations are azathioprine, carbamazepine, and codeine. The product labeling of both azathioprine and carbamazepine recommend consideration of genotyping before prescribing.[45,46] The labels of drugs containing codeine warn of potential side effects in people with certain genetic variations.[47]

Predicting Drug Effectiveness. Several drugs are subtherapeutic or ineffective in patients with genetic variations in genes that metabolize or are targets of the drugs. Clopidogrel (marketed as Plavix) is a platelet inhibitor often prescribed for secondary prevention following acute coronary syndromes and for those undergoing percutaneous coronary intervention. However, up to one quarter of patients taking clopidogrel experience a subtherapeutic antiplatelet response, resulting in a higher risk for ischemic events.[48,49] Clopidogrel is a prodrug; its antiplatelet properties are exerted once it is converted to an active metabolite that binds to specific platelet receptors.[50] A cytochrome P450 enzyme, CYP2C19, mediates the conversion of clopidogrel into the active metabolite. Genetic variations in *CYP2C19* can alter a patient's response to clopidogrel. Patients who carry those variations are considered poor metabolizers and show reduced ability to convert clopidogrel into its active metabolite, resulting in a diminished antiplatelet effect and increased chance for an ischemic event following clopidogrel therapy.[50,51] In 2009, the clopidogrel product labeling was revised to include *CYP2C19* genetic information. In 2009, a Boxed Warning was added to the labeling to warn about the reduced effectiveness of clopidogrel in patients who carry certain variations in *CYP2C19*, and to inform health care providers that genetic tests are available to detect these variations.[52]

Other important drugs that may be subtherapeutic or ineffective in patients carrying certain genetic variations are tamoxifen, used in the treatment and provision of estrogen receptor-positive breast cancer, and trastuzumab, used in the treatment of *HER2*-overexpressing breast tumors. In late 2006, an FDA advisory committee recommended including in the tamoxifen product labeling information about *CYP2D6* genotypes and potential effect on patient outcomes, and information on *CYP2D6* genotyping tests;[53] it has not yet been changed. The trastuzumab product labeling recommends genetic testing before prescribing the drug.[54]

Predicting Correct Dose. Genetic variations can lead to an altered dosage requirement for some drugs. Warfarin is metabolized by the CYP2C9 enzyme. Its anticoagulant effect is mediated by the enzyme VKORC1, which is the target enzyme inhibited by warfarin. Variation in the *CYP2C9* gene causes some patients to have slow metabolism of warfarin and a longer half-life of the drug, resulting in higher than usual blood concentrations of warfarin and greater anticoagulant effect. Certain variations in the *VKORC1* gene result in reduced activity of the enzyme and subsequently reduced function of vitamin K–dependent coagulation factors. The combination of slow metabolism of warfarin caused by *CYP2C9* gene variations and reduced coagulation caused by *VKORC1* gene variations increases the risk of bleeding during warfarin therapy.[55] Up to 40% of patients carry variations in either *CYP2C9* or *VKORC1*.[55]

The product labeling of warfarin has been modified twice since information about the genetic basis of its metabolism was discovered. In 2007, language was added cautioning that genetic variations in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin, and that lower initial doses should be considered for patients with genetic variations in *CYP2C9* and *VKORC1*. Early in 2010, the labeling was again updated to reflect the influence of genetics on dosage. The labeling now states "The patient's *CYP2C9* and *VKORC1* genotype information, when available, can assist in selection of the starting dose." The label includes a table describing the range of stable maintenance doses for patients with different combinations of *CYP2C9* and *VKORC1* variations.[56]

Direct-to-Consumer Genetic Testing

Direct-to-consumer (DTC) genetic testing refers to genetic tests that do not require the assistance of a physician or other health care provider to obtain. Types of genetic tests available directly to consumers include carrier testing; pharmacogenomic testing; and testing for susceptibility to complex diseases such as hereditary cancers; cardiovascular disease, and depression.[57-59] These tests are enabling consumers to obtain personalized health information without the benefit of a physician intermediary.

The AMA Board of Trustees studied the issue of direct-to-consumer genetic testing in Report 7 (A-08) "Direct-to-Consumer Advertising and Provision of Genetic Testing" (AMA Policy D-480.980, AMA Policy Database).[57] The AMA and several other medical professional societies are concerned that the risks associated with DTC genetic testing outweigh the benefits.[57,58,60-63] Among these risks is the challenge that the average patient faces in understanding the complex subject of genetics without a health care professional's guidance.[57] Nonetheless, consumers are interested in DTC genetic testing. In a recent survey of consumers, 70% of respondents had either used the services of a DTC genetic testing company (6%), or were interested in using such services in the future (64%).[64] In the same survey, 78% of respondents reported that they would seek help from a physician in interpreting test results.[64] Physicians should therefore be familiar with the types of DTC genetic testing available and their clinical validity and utility so that they are able counsel patients who have questions about the meaning of results.

CHALLENGES TO THE IMPLEMENTATION OF PERSONALIZED MEDICINE

As evidenced by the number of PM applications that are available to health care providers and consumers, the technology enabling PM is advancing rapidly. Yet there are challenges to its implementation in routine clinical practice. Among the challenges are the lack of genetics knowledge among health care providers, slow generation of clinical validity and utility evidence, a fragmentary oversight and regulatory system, and lack of insurance coverage of PM technologies.

Genetics Knowledge Among Health Care Providers

The successful uptake of genomic-based PM rests on health care providers' ability to understand and use it. Despite the current and future promise of genomics and PM for clinical practice, understanding and uptake of these new technologies has been slower than anticipated.[65] Surveys of primary care providers demonstrate a lack of basic knowledge about genetics and often, a lack of confidence in dealing with genetics-related issues that arise in the clinical setting.[66-69] A recent study concluded that health care providers cannot keep up with the pace of genetic tests and are not adequately prepared to use test information to treat patients appropriately.[30] In a recent survey of U.S. physicians conducted by the AMA and Medco, close to 90% of respondents indicated they did not have adequate information about genetic test availability and application in therapy. (AMA, unpublished data)

Especially troubling is the shortage of genetics professionals in the health care workforce. Fewer than 5,000 genetics professionals (medical geneticists and genetic counselors certified by the American Board of Medical Genetics or the American Board of Genetic Counseling) practice in the U.S.,[70,71] a number too low to meet the increasing demand for the anticipated rapid advances in genetic services. Primary care physicians and others outside of the traditional genetics specialties will likely be relied upon to provide genetic services.[72,73]

At the medical school level, uneven and inadequate genetics instruction has been identified as a significant barrier to the integration of PM into everyday medical practice.[74-76] An analysis of genetics content in medical school curricula found that 77% of schools taught genetics only in the first year, and that 47% did not incorporate any genetics content in the third and fourth years.[73] Deficiencies in genetics knowledge have been noted among medical students,[67,73,77] suggesting that current educational approaches need to be modified to better prepare students to use genomic technology once in practice.

Recommendations have been made to address the lack of genetics knowledge among health care providers. There is wide agreement that genetics education must be better incorporated into medical school and residency training, and made available as continuing education opportunities for practicing physicians.[65,66,78] Several organizations also have developed core competencies in genetics to guide the design of training programs for medical students, residents, and practicing health care providers.[13-15,79]

Among recommendations for pre-service training is to increase the attention devoted to genetics in common disease rather than rare single-gene disorders, since the treatment and prevention of common diseases will subsume the most time in clinical practice.[65] Such content should be presented both in genetics courses and also integrated into other courses focusing on organ systems and related disease processes, to underscore the contribution of genetics across all disease areas.[65] At the residency level, recommendations focus on connecting genetics and other specialties, such as joint residency programs combining medical genetics with other disciplines, and the development of genetics subspecialty fellowships within other residency programs.[65,80,81] Content in licensing exams could also be updated to reflect genetics content relevant to complex disorders in addition to current content on basic genetics.[80]

Continuing education for practicing physicians should contain information that will allow the physician to practice some genetic services and to determine when referral to a genetics professional is appropriate.[65,72,80] Keeping in mind the time constraints of busy physicians, resources that are Internet-based and designed to be used at the point of care, such as CDS linked

to EHRs, and a central repository that organizes clinical recommendations and practical tools to facilitate incorporation of genomics into routine practice, would be valuable to physicians.[65,80] Alternative models for learning, such as a learning collaborative similar to that used in the delivery of pediatric preventive services, have been proposed.[80,82] It has also been suggested that the maintenance of certification process be used to promote participation in genomic medicine-related activities by instituting genetics education requirements.[76,80] In 2010, plans for the creation of the Association of Genomic Medicine, a new board tasked with establishing an education curriculum for physicians that would lead to the accreditation of physicians in genomic medicine, were announced by the Scripps Translational Science Institute.[83]

Although competing demands and limited resources are challenges facing many organizations attempting to provide PM resources for their constituencies,[76] broad engagement of professional societies is critical to the implementation of PM in clinical care.[84] Professional organizations have been called upon to play an active role in encouraging and facilitating education and training in genomics.[70,74,82] They can also contribute by developing guidelines, opinion, policy statements, practice standards, and decision tools on PM, and host conferences that will offer opportunities for dialogue, workshops, and collaboration on PM topics.[30,84,85] Appendix II lists several educational resources for health care professionals wishing to learn more about basic genetics and the clinical implementation of genomic technologies.

Slow Evidence Generation

Genome-wide association studies (GWAS) have rapidly generated information about associations between genetic polymorphisms and disease. As of early 2010, almost 500 GWAS had been completed, yielding genetic information about common disorders such as diabetes, cardiovascular disease, depression, and asthma.[5,86] Combined with the results of other studies, there is now an astonishing amount of data about the genetic basis of disease. However, much of the data is preliminary, and often, the genetic polymorphisms identified account for relatively small portions of associated disease risk.[5] Nonetheless, tests that detect these polymorphisms are being developed for use in the clinic. Efforts to establish clinical validity and clinical utility are underway; in the absence of this evidence, health care providers must decide for themselves whether to use these tests to inform patient care. The lack of evidence about individual tests often leads health care providers to eschew genetic technologies altogether.[87]

The lack of evidence on clinical validity and utility has led some to believe it is still far too early to begin routine clinical implementation of genomic-based personalized medicine.[88] There is much discussion about what type of evidence should be required before a test is recommended for clinical use. Must it be generated by randomized controlled trials (RCTs), which are costly and lengthy? If only tests with a high level of evidence are deemed acceptable, then it could take years for genomic discoveries to be implemented in the clinic; conversely, if little evidence is required, practices could prematurely adopt new technologies that will have ill-defined consequences for patient care.[89,90]

Since genomic-based technologies are being developed rapidly, it is not practical to expect that evidence for every new technology will be generated by RCTs, nor should there be an expectation that funding will be available for RCTs.[90] Above all, impacts of testing on morbidity and mortality are central considerations in evaluating the clinical utility of genetic tests.[91] Additional considerations, such as psychosocial outcomes, are increasingly important but challenging to evaluate using traditional methods of evidence-based review.[91] Ultimately, test type and purpose may dictate what type of evidence is sufficient to establish clinical utility.[92] For example, clinical utility evidence for tests that diagnose rare, single-gene disorders will likely be limited to small-

scale studies since sample populations are inherently limited.[92] Conversely, for genetic susceptibility tests that are intended for larger-scale screening, more rigorous assessments of clinical utility will likely be required.[92]

Several groups have begun to review existing evidence surrounding selected genomic technologies and issue recommendations or guidelines. For example, the EGAPP (Evaluation of Genomics Applications in Practice and Prevention) Initiative was launched in 2004 by the Centers for Disease Control and Prevention's (CDC) National Office of Public Health Genomics. The EGAPP Initiative established a systematic, evidence-based process for assessing genetic tests and other clinical applications of genomic technology.[93] An independent, non-federal working group oversees the systematic review of evidence and makes recommendations based on that evidence. As of early 2010, EGAPP has commissioned several evidence reviews on the use of genetic tests that it believes have the potential for broad population impact,[94] and has issued recommendations on the use of four tests.[95] The United States Preventive Services Task Force (USPSTF) also occasionally reviews evidence and makes recommendations on the use of genetic testing in selected clinical situations.[96,97]

While the EGAPP process has been effective in reviewing genetic technologies and issuing recommendations, it does not have the resources to address every new genomic technology available to physicians. Similarly, the USPSTF does not focus solely on evaluating the use of genetic tests. Several recommendations for the creation of other review bodies have been made,[30,89,98] and the CDC's National Office of Public Health Genomics recently announced a funding opportunity for the creation of a Genomics Knowledge Synthesis Center, which would work collaboratively to plan and develop systematic evidence reviews on selected genomic applications, topic briefs on genomic applications, and methods to enhance the efficiency and quality of systematic evidence reviews.[99]

Oversight and Regulation of Genetic Tests

The system for regulating genomic-based PM technologies has been regarded as a barrier to clinical implementation since it largely fails to ensure that tests provide accurate and meaningful health information to physicians and patients.[30,89] The current oversight system leaves physicians and other health care providers to determine for themselves which genetic tests are available and the appropriate clinical scenarios in which to use them, and whether the test is clinically valid or useful.

Both the Centers for Medicare and Medicaid Services (CMS) and the FDA are charged with regulation of genetic tests and with oversight of the companies and laboratories developing the tests. All laboratories performing testing on human samples and reporting patient-specific results that have health implications are required to comply with the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which is administered by CMS.[100] CLIA requires that laboratories demonstrate a test's analytic validity, i.e., that the test accurately and reliably detects the analyte in question, and requires various types of performance assessment to verify analytic validity.[30] CLIA does not require that tests be clinically valid or have clinical utility. This means that physicians cannot infer that a genetic test will be informative for patient care just because it is being conducted in or offered by a CLIA-certified laboratory. Although most laboratories offering medical genetic testing in the U.S. are required to comply with CLIA, CMS does not make a listing of CLIA-certified laboratories publicly available.[101]

The FDA currently regulates only a small number of genetic tests that it considers "diagnostic test kits," which are tests consisting of multiple components that are bundled together and sold to

laboratories as a unit and typically require the use of complex, non-transparent algorithms to derive results. That type of test is FDA-cleared once information demonstrating analytic validity and clinical validity is submitted.[102] Only a fraction of genetic tests on the market fit into the "diagnostic test kit" category. The large majority of genetic tests are developed by and available from the laboratories themselves. Although the FDA believes it has the legal authority to regulate these laboratory-developed tests (LDTs), it has not exercised that authority.[103] Laboratories developing LDTs are subject to CLIA compliance and to the performance assessment requirements of other accrediting organizations to which they may belong, but except in a few specific circumstances, they are not required to demonstrate the test's clinical validity.[30]

In 2008, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) recommended that a mandatory, publicly available, online genetic test registry be created.[30] This registry would contain information about what genetic tests are available to health care providers and consumers, indications for use of tests, and about the analytic and clinical validity of tests, empowering physicians by providing them with reliable information about what is known and not known about genetic tests.[89,104] In March of 2010, the National Institutes of Health (NIH) announced that it will host a voluntary registry for genetic tests offered in the U.S.[105] The registry, available beginning in 2011, will function to encourage providers of genetic tests to enhance transparency by publicly sharing information about the availability and utility of their tests; provide an information resource for the public, including researchers, health care providers and patients, to locate laboratories that offer particular tests; and facilitate genomic data-sharing for research and new scientific discoveries.[105] Several medical professional organizations, including the AMA, test manufacturers, laboratories, and patient advocacy groups, have voiced support for a mandatory registry,[89] and some have urged that the newly announced NIH voluntary registry eventually become mandatory.[106]

Insurance Coverage of Genetic Tests

In a 2006 report, SACGHS stated that "…coverage and reimbursement are critical to ensuring appropriate access to genetic tests and services and their integration into clinical practice."[107] The number of genetic tests covered by insurance companies is limited. For a large number of genetic tests offered, patients must pay out-of-pocket, creating a barrier to the clinical implementation of genomic-based PM technologies. Physicians and health care providers are often reluctant to recommend a genetic test that is not covered by insurance and creates a financial challenge for particular patients.[107] Further, gaps in coverage result in health care disparities; those that can afford to pay for genetic tests out-of-pocket benefit from the health information, while those who cannot are effectively denied such information.[108]

In general, insurance company decisions about coverage are increasingly emphasizing evidence. Technology assessments that evaluate existing evidence on whether a genetic test is analytically and clinical valid and clinically useful, in addition to factors such as cost, are often used to guide coverage and reimbursement decisions.[107] Unfortunately, evidence needed to make informed coverage decisions is lacking for many genetic tests and services.[107] It has been suggested that the fragmentary regulatory system in place in the U.S., which does not require clinical validity or utility data before genetic tests are made available, acts as a disincentive for test developers to amass such data.[107] An analysis of factors influencing coverage decisions found that the strength of evidence was the strongest predictor of reimbursement.[109] Health care providers are demanding more evidence before implementing PM technologies;[87] combined with insurance companies' demand for evidence, genetic test developers may have more incentive to provide such evidence.

CMS policy states that screening tests performed "in the absence of signs, symptoms, complaints, or personal history of disease" are not covered by Medicare unless explicitly authorized.[107] Since CMS considers many genetic tests to be screening tests, they are not covered by Medicare. Additionally, Medicare coverage decisions are made both locally and nationally, creating variable coverage policies in regional areas. There is precedent for broadening Medicare coverage of preventive services; Congress has authorized coverage of screening tests such as mammography. In its report on coverage and reimbursement issues, SACGHS recommended that Congress add a Medicare benefit category for preventive services, which would allow CMS to consider covering more genetic tests.[107] It also recommended that CMS clarify that personal history of disease, a factor that is usually sufficient for coverage of screening tests, can include a family history of a disease.[107]

Medicare coverage decisions are closely monitored by private insurance companies, and often private insurers elect to cover tests or services if and when Medicare makes coverage decisions. However, with a few exceptions, genetic tests are often used for preventive, reproductive, and life-planning decisions, the majority of which happen before the age of 65. Therefore, the utility of genetic tests in the Medicare population may be lower than that in patients under the age of 65, and so private insurer reliance on Medicare decisions may not be appropriate in the case of genetic tests.[107]

There are signs that insurance companies are beginning to consider coverage of some genetic tests. In 2009, the Board of Directors of America's Health Insurance Plans (AHIP), an association representing more than 1,000 health insurance companies, issued a statement acknowledging that some genetic tests do improve health outcomes, and encouraging health plans to promote the availability of proven genetic tests.[110] Additionally, the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), which advises Medicare on coverage decisions by reviewing and evaluating effectiveness and appropriateness of medical services that are covered under Medicare or that may be eligible for coverage under Medicare, has recently discussed genetic screening tests and pharmacogenomic tests in cancer therapy.[111]

Medicare has recently begun to employ an alternative coverage strategy for promising treatments or technologies. Coverage with evidence development (CED) is a coverage option linked to a requirement that covered patients participate in data gathering by being enrolled in a clinical trial or registry that aims to determine the effectiveness of the technology or treatment.[112,113] For example, while Medicare does not generally cover the cost of *CYP2C19*/*VKORC1* genotyping to determine warfarin dose, it does cover the cost of the test for Medicare patients who are enrolled in NIH-sponsored trials assessing the clinical utility of *CYP2C19*/*VKORC1* genotyping.[114]

FEDERAL AND PRIVATE PERSONALIZED MEDICINE ACTIVITIES

Despite the challenges to implementing PM, there are a number of programs and activities at both the federal and private levels that focus on facilitating appropriate clinical implementation. Below are brief summaries of PM activities at the federal and private levels. PM also has been addressed in recent legislation.

Department of Health and Human Services

The majority of federal PM activities are occurring within the Department of Health and Human Services (HHS).[115] In 2006, the HHS Secretary launched the Personalized Healthcare Initiative, with the broad goals of: (1) linking clinical and genomic information to support personalized health care; (2) protecting individuals from discrimination based on unauthorized use of genetic

information; (3) ensuring the accuracy and clinical validity of genetic tests performed for medical application purposes; and (4) developing common policies for access to genomic databases for federally sponsored programs.[84,116] Several HHS agencies are involved in the implementation of these goals.

Food and Drug Administration. To date, the FDA has cleared several dozen genetic tests that it considers test kits.[102,117] Although FDA has chosen not to enforce regulation of LDTs, it has implemented a system to allow voluntary reporting of adverse events and malfunctions associated with LDTs.[118] During the last few years, the FDA moved toward increased regulation of genetic tests, evidenced by the release of a guidance for voluntary pharmacogenomic data submission, a draft guidance for pharmacogenomic and genetic tests, and a concept paper for the co-development of pharmacogenomic drugs and diagnostics.[4] Comments made by FDA officials confirm that the agency is developing at least four PM-related guidance documents that will be publicly available in 2010.[119] The FDA also regularly updates prescription product labeling with pharmacogenomics information.[4,41] Additionally, working with the NIH, the FDA has recently begun an initiative that aims to fast-track biomedical discoveries in PM and other sectors by funding research in regulatory science and ensuring that regulatory considerations are a key part of research planning.[120]

The Office of Clinical Pharmacology, located within the Center for Devices and Radiological Health at the FDA, is active in pharmacogenomics education initiatives for scientists and physicians.[121] In 2006, it collaborated with the AMA to develop the online CME "Pharmacogenomics and Personalized Medicine."

Centers for Medicare and Medicaid Services. CMS, which administers CLIA, plans to promote a more comprehensive approach to the oversight of genetic testing, including enhanced proficiency testing programs for laboratories and training for surveyors. It also plans to work with professional associations to promote the development of consensus guidelines and educational materials on genetic testing.[115] To expand the coordination of genetic testing oversight, CMS is collaborating with the CDC, FDA, NIH, and Federal Trade Commission toward future improvements.[113] However, at present, CMS has the authority under CLIA to regulate only laboratory performance; it does not have the authority to regulate tests themselves.

Centers for Disease Control and Prevention. The CDC's National Office of Public Health Genomics has been active in efforts to promote the appropriate clinical integration of PM technologies. Among its main projects are EGAPP,[93] and GAPPNet (Genomic Applications in Practice and Prevention Network), a collaborative project addressing the chasm between gene discoveries and their clinical validity and utility.[122] The GAPPNet project focuses on accelerating and streamlining the effective integration of validated genomic knowledge into the practice of medicine and public health by sponsoring research, evaluating research findings, and disseminating high-quality information on candidate genomic applications.[122] HuGENet (Human Genome Epidemiology Network) is an international project that promotes the integration and synthesis of epidemiological data describing interactions of genetic variants with modifiable risk factors and their contribution to disease.[123] The CDC is involved in several other activities contributing to PM, such as the National Program of Cancer Registries, the Genetic Testing Reference Materials Coordination Program, the National Newborn Screening Quality Assurance Program, and the Family History Public Health Initiative.[115]

National Institutes of Health. Several institutes within the NIH are working to further the science base that underlies PM technologies, and to develop resources for researchers aiming to translate basic science into clinical application and for health care providers who will encounter PM

technologies in the clinic. For example, The Cancer Genome Atlas, launched by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), is a collaborative project aimed at accelerating the understanding of the spectrum of genomic changes that occur in cancer.[115] The Cancer Biomedical Informatics Grid (caBIG) is an NCI initiative focused on realizing the potential of PM in improving patient outcomes by connecting data, organizations, and individuals to facilitate collaboration and speed research moving diagnostics and therapeutics from bench to bedside.[84] The Genomic Health Care Branch at the NHGRI promotes genetics literacy among the full spectrum of healthcare providers and their patients and serves as a liaison between the healthcare community and the NHGRI. The NHGRI directs the Ethical, Legal and Social Implications (ELSI) Research Program, which fosters basic and applied research on the ELSI of genetic and genomic research for individuals, families, and communities.[124] The NHGRI also recently launched the Genetics/Genomics Competency Center (G2C2), an online tool to help educators teach the next generation of nurses and physician assistants about genetics and genomics.[125]

U.S. Surgeon General. In 2004, the U.S. Surgeon General launched the Family Health History Initiative with the goal of helping all American families to learn more about their FHH.[126] Every year since 2004, the Surgeon General has declared Thanksgiving Day to be National Family History Day, during which families that have gathered together to celebrate the holiday are encouraged to talk about and to write down the health problems that seem to run in their family.[115] To support the initiative, My Family Health Portrait, a Web-based tool for individuals to enter FHH information that generates a record and pedigree that the individual can present to his or her physician, was developed. The most recent version of My Family Health Portrait generates pedigree information that is updateable and EHR-ready, and can be adopted by other organizations wishing to make a FHH tool available to patients and physicians.[19] The AMA has adopted the tool for use in its Care Coordination Platform for consumers, AMA-Health.org. The Surgeon General recently announced that My Family Health Portrait will be compatible with Microsoft's HealthVault personal health platform.[127]

Secretary's Advisory Committees on Genetics, Health, and Society. SACGHS is charged with: (1) assessing how genetic technologies are being integrated into health care and public health; (2) studying the clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications; (3) identifying opportunities and gaps in research and data collection analysis efforts; (4) analyzing uses of genetic information in education, employment, insurance, and law; and (5) serving as a public forum for discussion of issues raised by genetic and genomic technologies.[128] SACGHS has developed a number of reports on topics such as the U.S. system of oversight of genetic tests, coverage and reimbursement of genetic services, pharmacogenomics, gene patenting, and the education and training of health care providers in genetics.[30,76,107,129] Reports contain recommendations for actions by the Secretary that SACGHS believes would improve the use of genetic technologies in health care.

Personalized Medicine Activities of Non-Governmental and Private Organizations

Professional Organizations. A number of professional organizations representing health care providers have developed clinical practice guidelines on PM topics, and educational and point-of-care resources. The American College of Medical Genetics (ACMG) is arguably the most active professional organization providing genetics resources to physicians. It has published practice guidelines on several genetics subjects, policy statements, and standards for clinical laboratories; developed CMEs on genetic medicine; developed "ACT sheets," which describe the short-term actions a health professional should take in the care of an infant that has screened positive in the newborn screening panel; and holds an Annual Clinical Genetics meeting at which advancements

in the clinical use of genetic technologies are presented.[130] Other specialty professional organizations, such as ASCO, have developed practice guidelines and policy statements pertaining to genetics in their respective specialties.[62]

There is widespread belief that primary care physicians will encounter genetics issues and use genetic technology with increasing frequency.[65,72,73] Accordingly, professional organizations representing primary care physicians have been active in providing education and resources on genetics topics. In 2005, the American Academy of Family Physicians selected Genomics as its Annual Clinical Focus. As part of the focus, it provided publications and resources on FHH, familial cancers, newborn screening, ethical issues, pharmacogenetics, and inborn errors of metabolism.[131] The American Academy of Pediatrics focuses on providing education and developing policy on newborn screening topics and genetic disorders affecting children.[132] The American Congress of Obstetricians and Gynecologists provides education and helps in developing policy on genetic screening of pregnant and nonpregnant women and adolescents.[133] The AMA has developed several CME programs and educational resources; resources on genetics in routine clinical practice, pharmacogenomics, and hereditary cancers are currently under development.

Approximately 10 years ago, several professional organizations collaborated on the Genetics in Primary Care (GPC) project, aiming to enhance the ability of faculty to incorporate the clinical application of genetic information into undergraduate and graduate primary care medical education. GPC workgroups planned, implemented, and evaluated outcomes of training programs in genetics, targeting family medicine, general internal medicine, and general pediatrics faculty. The GPC project has had lasting effects on its participants' teaching and clinical practices.[134] A 2009 follow-up found that all faculty respondents reported having made changes to their formal and informal teaching practices, and that the majority reported changes to their clinical practice, including an increased awareness of genetics in clinical situations and more appropriate referral patterns.[134]

The pathologists and laboratory directors represented by the College of American Pathologists (CAP) are a valuable resource to physicians. CAP works to assist physicians in implementing PM by developing and providing diagnostic testing, interpreting and clearly reporting test results, integrating test information into clinical care with other health-care providers, and developing and promoting adherence to information standards.[135]

In addition to providing resources for health care providers, many professional organizations are involved in efforts to address policy issues surrounding genetics, such as appropriate regulation of genetic tests and ensuring the privacy of genetic information.

<u>The National Coalition for Health Professional Education in Genetics</u>. NCHPEG was established in 1996 by the AMA, American Nurses Association, and NHGRI, with the goal of integrating genetics content into the knowledge base of health professionals and students of the health professions.[136] NCHPEG develops educational tools and information resources that are accessible and useful to the target audience.[136] NCHPEG's members are an interdisciplinary group of individuals and leaders from more than 80 health professional organizations, consumer and volunteer groups, government agencies, private industry, managed care organizations, and genetics professional societies; a representative from the AMA has held a position on the NCHPEG Board of Directors since its inception.[136] NCHPEG has developed several resources for health professionals: genetics core competencies; educational programs on genetics in psychiatrics, genetics in race, and genetics in common complex disorders; and targeted genetics programs for non-physician health care providers such as physician assistants, speech-language

pathologists, dentists, and nutritionists.[136] It also holds an annual meeting focusing on a genetics topic relevant for primary care providers.

Institute of Medicine. In 2007, the Institute of Medicine (IOM), a division of the National Academies of Science, established the Roundtable on Translating Genomic-Based Research for Health. The Roundtable is made up of leaders from academia, industry, government, foundations, and associations who have a mutual interest in addressing the issues surrounding the translation of genomic-based research.[137] Its goal is to advance the field of genomics and improve the translation of research findings to health care, education, and policy.[137] The Roundtable holds regular workshops and has produced several reports based on the workshops, such as "Diffusion and Use of Genomic Innovations in Health and Medicine,"[138] "Innovations in Service Delivery in the Age of Genomics,"[139] and "Systems for Research and Evaluation for Translating Genome-Based Discoveries for Health."[140] An AMA representative holds a position on the Roundtable.

Personalized Medicine Coalition. The Personalized Medicine Coalition (PMC) is a group of approximately 150 federal agencies, clinical laboratories, diagnostic companies, biotechnology companies, patient advocacy groups, and research and educational institutions. The PMC works to advance the understanding and adoption of personalized medicine by collaborating with member organizations and outside experts to identify, analyze, and address ethical, legal and social implications of personalized medicine; providing a forum for debating public policy issues surrounding personalized medicine; educating policymakers and healthcare leaders about the importance of personalized medicine and its positive evolution; and, serving as an umbrella organization for stakeholders who are conducting personalized medicine research in both the public and private sectors.[141] The AMA is a member of the PMC.

Genetic Alliance. Genetic Alliance is an organization representing more than 1,000 genetic disease-specific advocacy groups, health care professionals, researchers, universities, and people affected by genetic diseases. It works to improve patients' health by fostering the integration of genetic advances into quality healthcare, public awareness, and consumer-informed public policies. It has created a number of resources for physicians, researchers, and consumers seeking to advance and utilize genetic technologies, such as a tool to evaluate the content, quality, and usability of educational materials, and a resource repository containing documents, links, audio, and video files on genetics-related topics. Genetic Alliance is also focused on advancing national policy that benefits people affected with genetic disorders; each year, it organizes "Genetics Day on the Hill," an event in which participants visit the offices of their elected officials to educate Congress about genetics in health and healthcare.[142]

Genetics and Public Policy Center. The Genetics and Public Policy Center (GPPC) was created in 2002 at Johns Hopkins University to help policymakers and the public understand the challenges and opportunities of genetic medicine. GPPC's goals are to develop and advocate for policies ensuring the safety and effectiveness of genetic tests and treatments; create models for fair systems of reimbursement to ensure broad access to genetic medicine and incentives for innovation; advocate for a high-throughput, responsive, and evidence-based system for creating, disseminating, and adopting medical and industry guidelines for genetic testing; protect genetic information so that the public feels safe taking a genetic test and participating in genetic research; and build public understanding of, and trust in, genetic medicine. GPPC has been especially active in advocating for proper regulation of genetic tests, including those available directly to consumers.[143]

Genetics in Federal Legislation

GINA. After approximately 12 years of advocacy efforts, the Genetic Information Nondiscrimination Act (GINA), was signed into law in 2008.[144] GINA, together with nondiscrimination provisions of the Health Insurance Portability and Accountability Act, generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or the individual's family members, or using it for decisions regarding coverage, rates, or preexisting conditions.[144,145] GINA also prohibits most employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment.[144,145] Until GINA was passed, there was little protection for patients wishing to keep their genetic information private from employers or insurance companies. There is now hope that those who resisted needed genetic tests because of fear that insurance carriers or employers could gain access to results will now be more willing to take advantage of the health information that testing offers.[146] While GINA offers significant protection from genetic discrimination, it does have shortcomings. For example, GINA does not protect against discrimination by life, disability, or long term-care insurers,[147] and it does not prohibit health insurers from using genetic test results in making health insurance payment decisions.[145] Also, the employment provisions of GINA do not generally apply to employers with fewer than 15 employees.[145]

ARRA Funding for PM Research. The American Recovery and Reinvestment Act (ARRA, 2009) contained funding opportunities for research into PM applications, with special emphasis on comparative effectiveness outcomes. Several applications proposing to study the comparative effectiveness of PM applications in cancer therapies were funded. For example, University of Pennsylvania researchers received funding to develop a coordinated, multidisciplinary center for the generation and synthesis of evidence to support the translation of genomic tests into improvements in cancer prevention, screening, diagnosis, treatment, and survivorship;[148] University of Southern California researchers received funding to undertake a large-scale collaborative effort that aims to uncover genetic predictors of prostate cancer in African American men;[149] and researchers at St. Jude Children's Research Hospital received funding for projects that will enable the first integrated genomic analysis of adolescent and young adult lymphoblastic leukemia.[150]

The Patient Protection and Affordable Care Act. The health system reform legislation recently signed into law contains provisions supporting research on PM. It creates a non-profit, independent Patient-Centered Outcomes Research Institute, which will conduct comparative effectiveness research. A key focus of the research will examine the utility and effectiveness of medical services in subpopulations, including those differentiated by genetic and molecular subtype.[151]

Personalized Medicine Implementation in Health Systems

PM has been recognized as offering potentially remarkable benefits in the delivery of care. Several community and academic health centers have begun investing in infrastructure that would support PM implementation and research programs aligned with the delivery of PM in patient care. Programs are aimed at increasing the use of genomics and other molecular techniques in clinical care, using HIT to integrate clinical care with research findings, and exploring methods to address the ethical, legal, and social implications of genomic medicine in patient care settings.[84] Included in Appendix III is a sample of health systems that have implemented PM.

CONCLUSIONS

It has long been recognized that individual patients respond to the same disease and treatments differently; Hippocrates said "It is far more important to know what person the disease has than what disease the person has."[4,152] The goal of PM is to identify these individual differences so that treatments and preventions can be tailored. However, there are challenges to implementing that goal. In order to maximize the benefit of PM technologies for patient care, several barriers need to be addressed. Most importantly, the health care workforce must become educated about the use of genetic technologies in clinical care and the potential benefits of PM. The amount of information known about the genetic basis of disease is growing rapidly and shows no sign of abating. Genomic-based clinical applications become available almost immediately, whether or not they are ready for clinical implementation. Knowledge about genetics will better prepare health care professionals to determine the appropriate use of PM technologies to enhance diagnosis and treatment. Also, better systems of oversight and regulation must be implemented, an exploration of the type of evidence that is sufficient to demonstrate clinical validity and utility should be undertaken, and coverage of clinically useful PM applications should be considered by insurers.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of this report be filed:

1. That our American Medical Association reaffirm Directives D-460.976, "Genomic and Molecular-based Personalized Health Care," and D-480.987, "Direct-to-Consumer Marketing and Availability of Genetic Testing." (Reaffirm HOD Policy)

2. That our AMA acknowledge the increasingly important role of genomic-based personalized medicine applications in the delivery of care, and will continue to assist in informing physicians about relevant personalized medicine issues. (New HOD Policy)

3. That our AMA continue to develop educational resources and point-of-care tools to assist in the clinical implementation of genomic-based personalized medicine applications, and will continue to explore external collaborations and additional funding sources for such projects. (Directive to Take Action)

4. That our AMA continue to represent physicians' voices and interests in national policy discussions of issues pertaining to the clinical implementation of genomic-based personalized medicine, such as genetic test regulation, clinical validity and utility evidence development, insurance coverage of genetic services, direct-to-consumer genetic testing, and privacy of genetic information. (New HOD Policy)

Fiscal Note: $20,000 to develop educational resources

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Appendix I. List of Acronyms

ACMG: American College of Medical Genetics
AHIP: America's Health Insurance Plans
AMA: American Medical Association
ARRA: American Recovery and Reinvestment Act
ASCO: American Society of Clinical Oncology
BCM: Baylor College of Medicine
caBIG: cancer Biomedical Informatics Grid®
CAP: College of American Pathologists
CDC: Centers for Disease Control and Prevention
CDS: clinical decision support
CED: coverage with evidence development
CLIA: Clinical Laboratory Improvement Amendments of 1988
CME: Continuing Medical Education
CMS: Centers for Medicare and Medicaid Services
CPGH: Center for Personalized Genetic Healthcare (Cleveland Clinic)
DTC: direct-to-consumer
EGAPP: Evaluation of Genomic Applications in Practice and Prevention
EHR: electronic health record
ELSI: ethical, legal, and social implications
FDA: U.S. Food and Drug Administration
FHH: family health history
FURTHeR: Federated Utah Research Translational Health e-Repository
GAPPNet: Genomic Applications in Practice and Prevention Network
GINA: Genomic Information Nondiscrimination Act
GMI: Genomic Medicine Institute (Cleveland Clinic)
GPC: Genetics in Primary Care
GPPC: Genomics and Public Policy Center
GWAS: genome-wide association study
G2C2: Genetics/Genomics Competency Center
HHS: U.S. Department of Health and Human Services
HIT: health information technology
HOD: AMA House of Delegates
HPCGG: Harvard Medical School-Partners Health Care Center for Genetics and Genomics
HuGENet: Human Genome Epidemiology Network
IOM: Institute of Medicine
LDT: laboratory-developed test
MEDCAC: Medicare Evidence Development and Coverage Advisory Committee
NCHPEG: National Coalition for Health Professional Education in Genetics
NCI: National Cancer Institute
NHGRI: National Human Genome Research Institute
NIH: National Institutes of Health
PBMC: peripheral blood mononuclear cells
PM: personalized medicine
PMC: Personalized Medicine Coalition
PRMP: Personalized Medicine Research Project (Marshfield Clinic)
RCT: randomized controlled trial
SACGHS: Secretary's Advisory Committee on Genetics, Health, and Society
TCC: Total Cancer Care (Moffitt Cancer Center)
USPSTF: United States Preventive Services Task Force

Appendix II. Selected Genetics Educational Resources for Health Care Providers.

Name of Resource:	Developed by:	Format:	Access:
Genetics in Clinical Practice: A Team Approach (2002, updated in 2010)	Dartmouth University, CDC, AMA	Online CME course (CME credit available)	TBD (contact pharmacogenomics@ama-assn.org)
Genetics and Your Practice (2003, updated in 2009)	March of Dimes	Online CME course (CME credit available)	http://www.marchofdimes.com/gyponline/index.bm2
PharmGenEd (2009)	UCSD Skaggs School of Pharmacy and Pharmceutical Sciences	Online CME course (CME credit available)	http://pharmacogenomics.ucsd.edu/home.aspx
Genetic Risk, Screening, and Intervention (2009)	American College of Preventive Medicine	Online CME course (CME credit available)	http://live.blueskybroadcast.com/bsb/client/CL_DEFAULT.asp?Client=446569&PCAT=1434&CAT=1434
The Future of Medicine: Pharmacogenomics (2008)	American College of Clinical Pharmacology	Online course (no CME)	http://user.accp1.org/Sample_Home.htm
Personalized health care report 2008: Warfarin and genetic testing (2008)	AMA, Critical Path Institute, and Arizona Center for Education and Research on Therapeutics	Brochure	http://www.ama-assn.org/go/warfarindosing
Surgeon General's Family History Initiative Resource Packet (2008)	U.S. Surgeon General	Web site	http://www.hhs.gov/familyhistory/respachealth.html
Pharmacogenomics and Personalized Medicine (2007)	AMA, FDA	Online CME course (CME credit no longer available)	http://ama.learn.com
Genetics in the Physician Assistant Practice (2007)	NCHPEG	Online CME course (CME no longer available)	http://pa.nchpeg.org/
ACMG Basics: Genetics for Providers (2007)	ACMG	CD-ROM CME course (CME no longer available)	http://www.acmg.net/AM/Template.cfm?Section=Terms_and_Conditions&termsreturnurl=Section=CME_Activities&Template=/CM/HTMLDisplay.cfm&ContentID=2856

Genetics and Common Disorders: Implications for Primary Care and Public Health Providers (2006)	NCHPEG	CD-ROM course (no CME)	Contact info@nchpeg.org to request a copy of the CD-ROM
Genetics in the Practice of Speech-Language Pathology and Audiology (2006)	NCHPEG	Online course (no CME)	http://shla.nchpeg.org/
Race, Genetics, and Health Care (2006)	NCHPEG	Online CME video presentation (CME no longer available)	http://www.nchpeg.org/content.aspx?sc=raceandgenetics&sub=1
Understanding Genetics: A Guide for Patients and Professionals (2006)	Genetic Alliance	Downloadable manual	http://www.geneticalliance.org/pubs-understanding-genetics-download
Genetics Through a Primary Care Lens (2005)	Genetics in Primary Care project	Web site	http://www.genetests.org/servlet/access?id=INSERTID&key=INSERTKEY&fcn=y&filename=/tools/index.html
GeneTests Educational Materials (regularly updated)	NIH, University of Washington	Web site	http://www.ncbi.nlm.nih.gov/projects/GeneTests/static/concepts/conceptsindex.shtml
Genetics and Genomics for Health Professionals (regularly updated)	NHGRI	Web site	http://www.genome.gov/27527599
Genetics Home Reference (for patients and consumers) (regularly updated)	National Library of Medicine	Web site	http://ghr.nlm.nih.gov/

Appendix III. Examples of Health System Implementation of PM. (Adapted from the U.S. Department of HHS report *Personalized Health Care: Pioneers, Partnerships, Progress*;[84] and from the Web sites of each medical center.)

Baylor College of Medicine (BCM). The Baylor Clinic and Hospital facilities, now under construction, were designed with the intent of fully delivering PM. BCM has developed an interactive, responsive EMR that includes CDS capable of integrating genetic information. Its Human Genome Sequencing Center and other faculty researchers have developed the BCM Chip, a diagnostic platform for pharmacogenomics testing, assaying risk for common complex diseases, human leukocyte antigen typing, single-gene disorder diagnosis, and predicting cancer susceptibility. Also, to prepare the next generation of health care providers for genomic medicine, BCM has developed new educational objectives and programs for all levels of medical training.[84]

Cleveland Clinic Genomic Medicine Institute/Center for Personalized Health Care. The Genomic Medicine Institute (GMI) serves as an expert base for the principles and practice of genomic medicine as a single platform for research, academic clinical care, and outreach and education ultimately directed at genomics-based personalized healthcare. The clinical branch of the GMI is the Center for Personalized Genetic Healthcare (CPGH). Working closely with a patient's physician and other departments within the Cleveland Clinic, the CPGH team addresses healthcare issues with patients who have, or are at risk to have, inherited conditions. Services are available at satellite Cleveland Clinic locations as well.[153]

El Camino Hospital Genomic Medicine Institute (Silicon Valley, CA). El Camino Hospital has begun to provide the necessary impetus and infrastructure to accelerate the process of adoption of genomics for the benefit of its patients. Its three-pronged approach is to identify genetic and genomic tests that are most appropriate for patients, support their integration into clinical practice, and provide educational and counseling support to patients.[154]

Fox Chase Institute for Personalized Medicine (Philadelphia, PA). In 2009, Fox Chase Cancer Center launched the Institute for Personalized Medicine, a program aiming to match targeted drug therapies to the genetic profiles of individual patient tumors on a large scale. Fox Chase has already established a substantial Biosample Repository and Tumor Bank that will serve as a component to the program. The genetic information to be gathered about individual patient tumors offers the possibility of individualizing cancer treatments selected for patients.[155]

Geisinger Health System (Danville, PA). Geisinger Health System's personalized medicine program is an initiative to re-engineer the paradigm of healthcare from reactive to predictive and, with the help of researchers and physicians, engage patients in their personal health and wellness. A program at Geisinger, MyCode, is capitalizing on the health system's ability to link genomic information with its advanced electronic health record system and growing biobank. MyCode is a tool aiming to match genes with a comprehensive profile of a specific chronic condition, enabling researchers to study groups of patients with similar signs and symptoms and predict and understand how they will respond to specific treatments.[156]

Harvard-Partners. The Harvard Medical School-Partners Health Care Center for Genetics and Genomics (HPCGG) was founded several years ago to enhance the Partners HealthCare System infrastructure and to speed adoption and improve the quality of PM. HPGCC has created facilities that support research activities and a CLIA-certified molecular diagnostic laboratory offering gene-based tests to health care providers.[84] HPGCC also has deployed an information

technology infrastructure that links together the research facilities, laboratory, and the Partners HealthCare EMR.[84]

Marshfield Clinic (Marshfield, WI). The Marshfield Clinic has been engaged in both PM research and delivery. In 2002, Marshfield Clinic launched the Personalized Medicine Research Project (PRMP) as a catalyst for implementation of PM in the clinic. PRMP has enrolled over 20,000 adults in a project designed to support research into pharmacogenomics, genetic basis of disease, and population genetics. Marshfield's clinical delivery of PM, informed by the PRMP, is supported by its Medical Genetic Services Department that provides clinical genetic consulting and genetic counseling, its molecular diagnostic laboratory, and genetics educational programs for its physicians and patients.[84]

Moffitt Cancer Center (Tampa, FL). Moffitt Cancer Center has developed the Total Cancer Care (TCC) program, made up of a large cancer biorepository and an information system containing patients' clinical outcomes data, with the goal of discovering biomarkers for the identification of high risk populations, early detection, predictors of therapy response, and clinical trial matching. There are now more than 20,000 patients from 16 clinical sites enrolled, and a central data warehouse containing biorepository, cancer registry, and clinical and molecular profiling data, is in place with portals to access it for researchers, physicians, and patients planned.[84]

Ohio State University Center for Personalized Health Care. The Ohio State University Center for Personalized Health Care is aimed at supporting research, education and translation of personalized medicine. Projects within the Center focus on biomedical informatics, cancer genetics, pharmacogenomics, and research data management.[157]

University of Utah/Intermountain Healthcare. The University of Utah (U of U) has begun the Federated Utah Research Translational Health e-Repository (FURTHeR), an informatics infrastructure that will link genotypic, phenotypic, genealogic, clinical, environmental, and public health data from disparate sources statewide and make them available to health care providers through a Web-based portal. This is partly possible because of the Utah Population Database, which contains genealogy, demographic, and kinship information for more than one million individuals in 170,000 families.[84]