PMC Personalized Medicine Coalition

The Case for

PERSONALIZED MEDICINE

We shed light on the demonstrated benefits of personalized medicine and describe the pathway for its widespread adoption to improve healthcare.

EXECUTIVE SUMMARY

A tectonic shift is taking place in medicine. For the average patient the movement is subtle, perhaps imperceptible, but ultimately it will affect the entire landscape of our healthcare system. Since the mapping of the human genome in 2003, the pace of discovery, product development, and clinical adoption of what we know as personalized medicine has accelerated.

Personalized medicine may be considered an extension of traditional approaches to understanding and treating disease, but with greater precision. A profile of a patient's genetic variation can guide the selection of drugs or treatment protocols that minimize harmful side effects or ensure a more successful outcome. It can also indicate susceptibility to certain diseases before they become manifest, allowing the physician and patient to set out a plan for monitoring and prevention. Physicians can now go beyond the "one size fits all" model of medicine to make the most effective clinical decisions for individual patients.

We can now point to real-world examples of almost every aspect of personalized medicine's promise to refine diagnosis, guide optimum treatment, and avoid unnecessary side effects.

Personalized medicine offers a structural model for efficient healthcare. It is preventive, coordinated, and evidence-based. It relies on a network of electronic health records that link clinical and molecular information to help patients and physicians make optimal treatment decisions. It is proactive and participatory, engaging patients in lifestyle choices and active health maintenance to compensate for genetic susceptibilities.

Substantial progress has been made towards the implementation of personalized medicine. When all of the pieces of infrastructure fall into place; when we begin to classify and treat diseases not just by their most obvious signs and symptoms, but also by their molecular profiles; when physicians combine their knowledge and judgment with a network of linked databases that help them interpret and act upon a patient's genomic information; when insurance companies pay for tests and treatments that anticipate the needs of the patient as much as react to them; and when regulators insist on using all information available to the physician, including genetic tests, to ensure the safety and efficacy of an approved drug, then "personalized medicine" will be known, simply, as medicine.

THE CURRENT LANDSCAPE

What Is Personalized Medicine?

"Personalized medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

President's Council of Advisors on Science and Technology (PCAST) "Priorities for Personalized Medicine"
September 2008[1]

Personalized medicine may be considered an extension of traditional approaches to understanding and treating disease. Physicians have always used observable evidence to make a diagnosis or prescribe a treatment tailored to each individual. In the modern conception of personalized medicine, the tools provided to the physician are more precise, probing not just the visually obvious, such as a tumor on a mammogram or the appearance of cells under a microscope, but the very molecular makeup of each patient. A profile of a patient's genetic variation can guide the selection of drugs or treatment protocols that minimize harmful side effects or ensure a more successful outcome. It can also indicate susceptibility to certain diseases before they become manifest, allowing the physician and patient to set out a plan for monitoring and prevention. The ability to profile the structure, sequence, and expression levels of genes, proteins, and metabolites is redefining how we classify diseases and select treatments, allowing physicians to go beyond the "one size fits all" model of medicine to make the most effective clinical decisions for each patient.

It is an approach that is well suited to the medical challenges faced in the 21st century. Although we have prevailed over many of the diseases that have plagued humanity throughout the ages, what remains are diseases of greater complexity: diabetes, cancer, heart disease, and Alzheimer's disease. They are not caused by a single gene or a single event but by a combination of genetic and environmental factors, and they tend to be chronic, placing a heavy burden on the healthcare system. Personalized medicine provides the tools needed to better manage chronic diseases and treat them more effectively.

> "It's far more important to know what person the disease has than what disease the person has."
>
> *Hippocrates*

We can now point to real-world applications of almost every aspect of personalized medicine's promise: Genetic profiles can better discern different subgroups of breast cancer, guiding physicians to select the best treatment protocol or, in some cases, forego the expense and risks of chemotherapy altogether;[2] tests detecting variation in the way individuals metabolize the blood thinning drug warfarin can help predetermine the right dose for a patient, navigating the narrow therapeutic passage between reducing risk of clots, and triggering internal bleeding.[3] A test for mutations in the genetic coding for an enzyme can help physicians select the most effective drug for a colon cancer patient from an expanding pharmacopoeia of choices, avoiding a costly and protracted trial and error approach that can leave the patient suffering needlessly from adverse effects or losing precious time in battling the disease.[4,5]

As evidence of the benefits continues to grow, an infrastructure of laws, policy, education, and clinical practice is building around personalized medicine to support its use:

- Medical institutions across the country have announced their commitment to putting personalized medicine into practice through dedicated Centers or statewide initiatives.
- Personalized medicine approaches are

"Over the past decade, we have unlocked many of the mysteries about DNA and RNA…This knowledge isn't just sitting in books on the shelf nor is it confined to the workbenches of laboratories. We have used these research findings to pinpoint the causes of many diseases, such as sickle cell anemia, cystic fibrosis, and chronic myelogenous leukemia. Moreover, scientists have translated this genetic knowledge into several treatments and therapies prompting a bridge between the laboratory bench and the patient's bedside."

Senator Barack Obama (D–Ill.)
Introductory remarks on the Genomics and Personalized Medicine Act (S.976)
March 23, 2007

becoming "best practice" in hospitals, in order to ensure that patients with serious conditions such as cancer are given the optimum therapy from the start.

- The regulatory system is integrating genetic testing into the labels of pharmaceutical products, ensuring that a drug is administered in a way that minimizes the risk of adverse effects and improves the chances of effective treatment.[6]

- Nearly every major pharmaceutical development project is incorporating information on genetic variation and its effects on the safety and effectiveness of the candidate drug.

- Personalized medicine applications have extended beyond cancer to improve treatments in cardiovascular disease, infectious diseases, psychiatric disorders, and transplantation medicine.

- Several of the nation's leading medical schools are launching genomics-based medical education programs to train the next generation of care providers.

- The American Association of Health Plans has advocated policy encouraging genetic testing and preventive care, while several large private insurers have begun paying for genetic tests identifying presymptomatic high-risk populations.

- The U.S. Department of Health and Human Services (HHS), the President's Council of Advisors in Science and Technology (PCAST), and the Personalized Medicine Coalition (PMC) have defined wide-ranging policy recommendations for personalized medicine; a genetic privacy law has been passed, and other legislation supporting personalized medicine has been introduced in the U.S. Senate and House of Representatives.

MILESTONES *in Personalized Medicine*

1898
Sir Archibald Garrod coins the term "chemical individuality" to describe inherited predispositions to metabolizing sulphonal drugs.

1900
Gregor Mendel's work, conducted in 1865 and largely ignored, is rediscovered, launching the genetic era.

1902
Lucien Cuenot advances the hypothesis that genetically determined differences in biochemical processes could be the cause of adverse reactions after the ingestion of drugs.[7]

1941
The relationship between genes and the production of proteins is discovered.

1956
The "chemical individuality" hypothesis is proven when a genetic deficiency of glucose-6-phosphate dehydrogenase is found to be linked to antimalarial primaquine toxicity.[8]

CLINICAL APPLICATIONS

Ultimately, the success of personalized medicine will rise or fall on its ability to demonstrate its value—to the healthcare system, to the industries that develop its products, and to patients. The promise of personalized medicine, for which tangible evidence already exists, includes the ability to:

- Shift emphasis in medicine from reaction to prevention
- Enable the selection of optimal therapy and reduce trial-and-error prescribing
- Make the use of drugs safer by avoiding adverse drug reactions
- Increase patient compliance with treatment
- Reduce the time and cost of clinical trials
- Revive drugs that are failing in clinical trials or were withdrawn from the market
- Reduce the overall cost of healthcare

Shift Emphasis in Medicine from Reaction to Prevention

Personalized medicine introduces the ability to use molecular markers that signal the risk of disease or its presence before clinical signs and symptoms appear. This information underlies a healthcare strategy focused on prevention and early intervention, rather than a reaction to advanced stages of disease. Such a strategy can delay disease onset or minimize symptom severity. One example is a test used to look for *BRCA1* and *BRCA2* genetic mutations indicating a hereditary propensity for breast and ovarian cancer.[16] Women with *BRCA1* or *BRCA2* genetic risk factors have a 36 to 85 percent lifetime chance of developing breast cancer, compared with a 13 percent chance among the general female population.[17,18,19] For ovarian cancer, women with certain *BRCA1* or *BRCA2* gene mutations have a 16 to 60 percent chance of disease, compared with a 1.7 percent chance among the general population. The *BRCA1* and *BRCA2* genetic test can guide preventive measures, such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

Over 1300 genetic tests exist that signal inherited susceptibility to conditions as

"The pharmacogenetic approach is used for almost every compound we develop… We are now looking for markers for response and for adverse events to better understand our current compounds and to improve effectiveness of future compounds."

Paul Stoffels, M.D.
Company Group Chairman, Global Pharmaceutical Research and Development Johnson & Johnson

wide ranging as hearing loss and sudden cardiac arrest. While not every test has a therapeutic option, a genetic diagnosis often permits targeted prevention or mitigation strategies.

Select Optimal Therapy

On average, a drug on the market works for only 50 percent of the people who take it.[20] (Figure 1) The consequences in terms of quality and cost of care are significant, leaving patients to contend with their disease and their medical bills as they switch from one drug to another until they find an effective therapy. Studies have linked differences in response to the differences in genes that code for the drug-metabolizing enzymes, drug transporters,

or drug targets.[21,22,23] The use of genetic and other forms of molecular screening allows the physician to select an optimal therapy the first time and avoid the frustrating and costly practice of trial-and-error prescriptions.

One of the most common applications of personalized medicine has been for women with breast cancer. About 30 percent of breast cancer cases are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor 2 (HER2). For these women, standard therapy is not effective, but one treatment does work—an antibody drug called Herceptin® (trastuzumab).[24,25] Herceptin

can actually reduce the recurrence of a tumor by 52 percent when used in combination with chemotherapy, compared to chemotherapy alone. Molecular diagnostic tests for HER2 are used to identify the 30 percent of patients who will benefit from receiving the drug.

Another test, Onco*type* DX®, can be used to determine whether women with certain types of breast cancer are likely to benefit from chemotherapy.[26,27,28] The test measures the expression of 21 genes and yields a score that places the patient into one of three categories: low, intermediate, or high risk of having a tumor return within 10 years. A patient with a low risk of tumor recurrence may be treated successfully with hormone therapy alone, avoiding the expense and toxic effects of chemotherapy. A patient with a high risk of recurrence might be better off undergoing more aggressive treatment with chemotherapy.
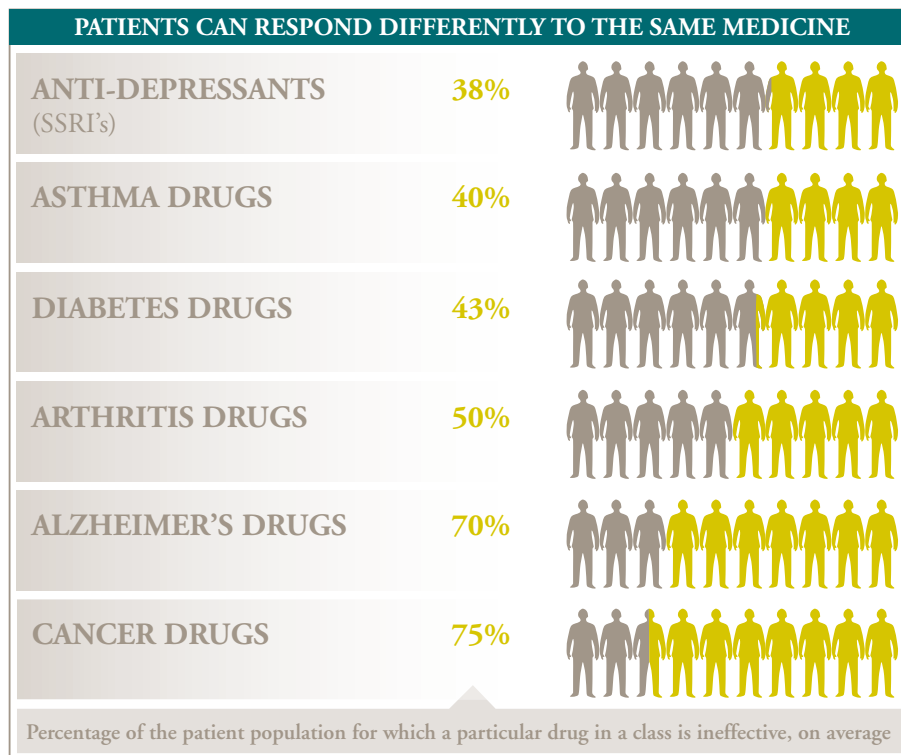
A growing number of drugs have become available for the treatment of colon cancer, some of which are best selected using a genetic test. About 40 percent of patients with metastatic colon cancer are unlikely to respond to two of these drugs, Erbitux® (cetuximab) and Vectibix® (panitumumab), because their tumors have a mutated form of the *KRAS* gene.[29] Current practice guidelines recommend that only patients with the normal form of the *KRAS* gene should be treated with these drugs along with chemotherapy.[30] The *KRAS* gene is also considered in the selection of treatment for lung cancer.[31]

Make the Use of Drugs Safer

According to a review of several studies, about 5.3 percent of hospital admissions are associated with adverse drug reactions (ADRs).[32] Many ADRs are the result of variations in genes coding for the cytochrome P450 (CYP450) family of enzymes and other metabolizing enzymes.[33,34] These variants may cause a drug to be metabolized more quickly or slowly than in the general population. As a result, some individuals may have trouble eliminating a drug from their

Figure 1: One Size Does Not Fit All

PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE		
ANTI-DEPRESSANTS (SSRI's)	38%	
ASTHMA DRUGS	40%	
DIABETES DRUGS	43%	
ARTHRITIS DRUGS	50%	
ALZHEIMER'S DRUGS	70%	
CANCER DRUGS	75%	

Percentage of the patient population for which a particular drug in a class is ineffective, on average

Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, Pages 201-204.

Milestones in Personalized Medicine

1959
The term "pharmacogenetics" is coined by the German geneticist Friedrich Vogel.

1967
The genetic code is cracked, revealing how DNA sequences code for protein.

1975
Gene sequencing techniques are invented.

1977
Metabolism of drugs by enzymes of the CYP450 system is identified as a key genetically determined cause for variation in drug response.[9]

1983
A polymerase chain reaction technique is invented for *in vitro* amplification of DNA sequences.

> *"Healthcare today is in crisis as it is expensive, reactive, inefficient, and focused largely on one size fits all treatments for events of late stage disease. An answer is personalized, predictive, preventive, and participatory medicine."*
>
> *Ralph Snyderman, M.D.*
> *Chancellor Emeritus, Duke University*
> *Founder and Chairman, Proventys*

bodies, leading in essence to an overdose as it accumulates, while others eliminate the drug before it has a chance to work. The consequences of not considering variation in these genes when dosing can range from futility to unpleasant or even fatal side effects.

The U.S. Food and Drug Administration (FDA) has approved the Amplichip® CYP450 test, a microarray device that can detect 29 variations in two important CYP450 genes, *CYP2D6* and *CYP2C19*, which are linked to the metabolism of about 25 percent of all drugs prescribed.[35] The information provided by Amplichip and similar tests is already helping physicians make better decisions about drug treatments and dosages.

The UGT1A1 assay™, which tests variation in an enzyme called UDP-glucuronosyltransferase, was also approved by the FDA to predict patients' safety-related responses to Camptosar® (irinotecan), which is used to treat colon cancer.[36] The test allows physicians to adjust the irinotecan dosage for the approximately 10 percent of patients who metabolize the active form of the drug too slowly, which would lead to toxic accumulations in the bloodstream.

Administration of the drug warfarin, used to prevent blood clots, is complicated by genetic variations in a drug metabolizing enzyme (CYP2C9) and a vitamin K activating enzyme (VKORC1). Dosing is typically adjusted for the individual patient through multiple rounds of trial and error

throughout the first year of treatment, during which time the patient may be at risk of excessive bleeding or further blood clots. The need to get warfarin dosing right the first time to avoid adverse effects led the FDA to recommend genotyping for all patients before receiving treatment with warfarin.[37]

Increase Patient Compliance to Treatment

Patient non-compliance to treatment leads to adverse health effects and increased costs. When personalized therapies prove more effective or present fewer side effects, patients will be more likely to comply with their treatments. The greatest impact could be for the treatment of diseases such as asthma and diabetes, in which non-compliance commonly exacerbates the condition. At least one study supports this point. Inherited forms of hypercholesterolemia (high cholesterol) can increase the risk of myocardial infarction before the age of 40 more than 50-fold in men and 125-fold in women. Conventional monitoring of cholesterol levels can catch the condition early, but genetic testing offers additional benefits. In addition to detecting the condition before there are observable signs of disease, knowledge of a genetic predisposition for hypercholesterolemia provides patients with a powerful incentive to make lifestyle changes and to treat their condition seriously. Patients with a genetic diagnosis have shown more than 86 percent adherence to their treatment program after two years compared to 38 percent prior to testing.[38]

Reduce Time, Cost, and Failure Rate of Clinical Trials

Developing a new drug is a costly and lengthy process.[39] Theoretically, the use of pharmacogenomic data, or information about how patients' genes affect their drug responses, could reduce the time and cost of drug development in addition to reducing the rate of drug failures by allowing researchers to focus on sub-sets of patient populations. Using genetic tests, researchers could preselect patients for studies, using those most likely to respond or least likely to suffer side effects. Enriching the clinical trial pool, as this approach is called, could reduce the size, time, and expense of clinical trials.

Anecdotal evidence suggests that pharmacogenomics can cut the length of clinical trials as well. For example, a phase III clinical trial for the drug Tykerb® (lapatinib) was terminated early due to the drug's remarkable success in treating a molecularly defined subset of patients with breast cancer.[40] The drug was subsequently approved for use in combination with capecitabine for certain HER2-positive patients.

Bucindolol is a beta blocker that was being tested for the treatment of heart disease, but it was dropped by its maker years ago after it failed to demonstrate any effectiveness over placebo.[41] Since then, scientists have developed a genetic test, called the Beta-blocker Evaluation of Survival Test (BEST) that can predict which patients will actually benefit from

the drug. A new study using the genetic test provided much clearer evidence of bucindolol's effectiveness in a sub-population (about 50 percent) of heart patients. The drug reduced heart disease deaths by 48 percent (compared to standard beta blockers which cut death rates by 35 percent), and hospitalizations for heart failure by 44 percent.[42]

Reduce the Cost of Healthcare

The cost of healthcare in the United States is on an unsustainable upward climb. Incorporating personalized medicine into the fabric of the healthcare system can help resolve many embedded inefficiencies, such as trial-and-error dosing, hospitalization of patients who have severe reactions to a drug, late diagnoses, and reactive treatment. Specific examples of personalized medicine are generating tangible results about their economic benefit.

Authors of a recent study exploring potential healthcare cost savings from using genetic testing estimated that the use of a genetic test to properly dose the blood thinner warfarin could prevent 17,000 strokes and 85,000 "serious bleeding events" each year and avoid as many as 43,000 visits to the emergency room. If the 2 million people that start taking warfarin each year were to be tested at a cost of $125 to $500 per patient, the overall cost savings to the healthcare system would be $1.1 billion annually. [43] Similarly, researchers showed in a 2006 article published in *Cancer* that adjusting dosage of the colon cancer drug irinotecan based on *UGT1A1* testing results in about $1,000 in savings per patient tested by reducing adverse events.

An economic analysis of the Onco*type* Dx test looked at the real costs of treating women with breast cancer in a 2 million member health plan. If half of the 773 eligible patients received the test, then the savings in terms of adjuvant chemotherapy, supportive care and management of adverse events would be about $1930 per patient tested (based on a 34 percent reduction in chemotherapy use). [44]

A new study has found that $604 million could be saved annually if Vectibix (panitumumab) or Erbitux (cetuximab) were limited to those patients with metastatic colorectal cancer whose *KRAS* gene is not mutated, because those are the only patients who benefit from the drugs.[45]

"The key to fixing America's broken healthcare system is to measure the value of healthcare instead of its cost…Individualized medicine, including biomarkers for tamoxifen and warfarin sensitivity and gene signature studies that are identifying other drug sensitivities in patients, can significantly improve the value we deliver to patients."

Denis A. Cortese, M.D.
President and Chief Executive Officer,
Mayo Clinic

1990
The Human Genome Project is launched.

September 1998
Herceptin®, a drug that works on a 25 percent subpopulation of breast cancer patients, is approved by the U.S. Food and Drug Administration (FDA). On the same day, the HER2 test identifying the target population is also approved.

April 2003
The sequencing of the human genome is declared complete after 13 years and a $3 billion investment.

May 2004
The Office of the National Coordinator for Health Information Technology is established.

November 2004
The Personalized Medicine Coalition (PMC) is launched with 18 members from industry, government, and academia.

THE TECHNOLOGY INFRASTRUCTURE

The evidence of the benefits of personalized medicine is accumulating rapidly, and the real-world applications of this knowledge are beginning to grow as well. Three areas of technology are key to making personalized medicine a ubiquitous presence in our healthcare system: 1) new tools to decode the human genome; 2) large-scale studies and sample repositories that help link genetic variation to disease and response to therapy; and 3) a healthcare information technology infrastructure that supports the integration of research and clinical data, as well as the ability of physicians to track and tailor every aspect of patient care according to genetic and molecular profiles. In addition, technology advances have

enabled personalized medicine to be brought to the public through the use of personal genetic testing.

The Tools

Automated systems for sequencing DNA or spot-checking for genetic variation are essential to progress in both research and clinical applications. DNA microarrays borrow technology from integrated circuit manufacturing, enabling scientists to detect hundreds of thousands of genetic variations on a single chip and are instrumental in identifying which variations are associated with specific diseases. In the last five years, the number of single nucleotide polymorphisms (SNPs, changes in single DNA chemical building blocks of the genome) that can

be examined in a 1 cm^2 chip increased from 250,000 to 920,000. It is estimated that there are 10 million such variations in the human genome.

There are many "omics" that are being studied as possible tools in personalized medicine. Genomics and transcriptomics offer information on genetic variation and the level of gene expression. Proteomics looks at the entire complement of proteins expressed by cells. Metabolomics examines the small molecules that are the byproducts of chemical reactions in our bodies.

What was once thought to be a single disease characterized by a common set of physical signs and symptoms (such as breast cancer or asthma) may be several

Figure 2: The Shrinking Cost of DNA Sequencing—Toward the $1000 Genome
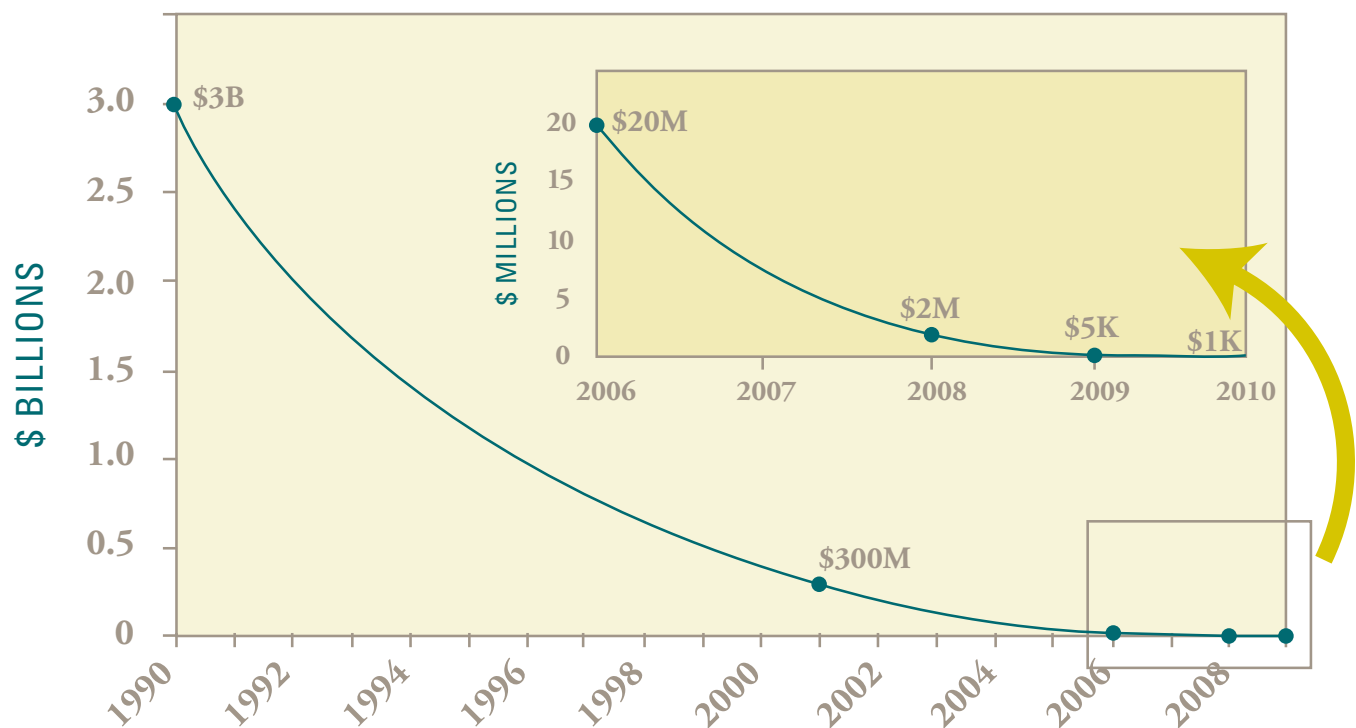
Sources: Wheeler DA et al., Nature 2008; 452:872-6; Mardis E. Genome Biology 2006; 7:112; Keim B. Wired Science October 06, 2008; The 2009 and 2010 values are projected. Current cost of complete genome sequencing (as of April 2009) is $60,000 (Applied Biosystems).

distinct conditions, or it could be a single disease with a spectrum of treatment options, depending on the risk profile of the individual patient.

In the area of blood cancers, for example, there were only two diagnoses available in the 1920s—leukemia and lymphoma. Today, cellular and genetic analyses can distinguish 38 types of leukemia and 51 types of lymphoma. A better understanding of the nuanced differences between the categories of cancer has guided more effective drug development and more appropriate strategies for treatment. As a result, survival rates for many of the subtypes of blood cancer have improved from 0 percent to as high as 90 percent.[46]

Proponents of personalized medicine envision a future in which each person, at birth, is provided with his/her full genomic sequence to place into a personal medical record. The information from a personal genome would allow physicians to develop a more holistic, proactive healthcare strategy based on the patient's susceptibility to different diseases and reactions to different types of medicine. Advances in genomic sequencing are clearly on an exponential curve, and many scientists believe that with the help of private and public investment the $1000 genome will arrive in a few years (Figure 2).[47,48]

Large-Scale Studies and Supporting Resources

To make a genetic sequence clinically useful, it is essential to find associations between specific genetic markers and a disease or drug response. Such studies usually require thousands of participants and the collection and preservation of a large number of biological specimens and genetic material, and as such can go well beyond the resources of a single company or laboratory. That is why the second

major area of technology infrastructure for personalized medicine—large-scale population studies to link genetic and molecular signatures to disease and its treatment—must be supported by partnerships between public and private institutions.

A growing number of endeavors co-sponsored by government, academia, and industry have begun to generate publicly available data and frameworks to support large-scale genome-wide disease association studies and future personalized medicine products and practices. Among them are the International HapMap Project; the Database of Genotype and Phenotype (dbGAP); the Genetic Association Information Network (GAIN); The Biomarkers Consortium; the Genes, Environment and Health Initiative; The Cancer Genome Atlas; and the Serious Adverse Events Consortium.

Health Information Technology

Health Information Technology (HIT) is pivotal to the advancement of personalized medicine. Without the ability to bring together, analyze, and organize information that can help illuminate each person's unique biology and medical history, compare it with large-scale clinical outcomes information, and thereby predict risks and responses to treatments, it is not possible to individualize healthcare.

Recent studies suggest that the adoption of HIT solutions like electronic health records (EHRs) is lagging behind scientific and clinical advancements in personalized medicine. The evidence varies, but perhaps as few as two percent[49] or as many as 11 percent of hospitals,[50] and less than five percent of solo physicians[51] have implemented fully operational EHRs.

The Obama administration and Congress have made nationwide implementation of standardized healthcare IT a top

priority by including an unprecedented $19 billion in funding as part of the Health Information Technology for Economic and Clinical Health Act, or HITECH Act, section of the American Recovery and Reinvestment Act of 2009 (ARRA). In 2004, a presidential executive order established the Office of the National Coordinator for Health Information Technology (ONC), calling for the nationwide implementation of interoperable EHRs within 10 years. The ARRA legislation permanently establishes this office within HHS and provides significant resources to meet President Obama's goal for every American to have an EHR by 2014.[52]

In addition, government initiatives —such as the National Cancer Institute's cancer Biomedical Informatics Grid® (caBIG®) initiative begun in 2004—have started to connect the biomedical research community (including government institutes, academic medical centers, and private sector companies developing treatments and diagnostics) together with clinical care centers to enable information sharing to speed the translation of research discoveries into patient care and allow clinical outcomes to circle back to continuously inform biomedical research.[53]

Several healthcare delivery organ-izations—academic, non-profit, and governmental —are already putting EHRs into practice to support personalized medicine for their patients. For example, Partners Healthcare, together with the Harvard Medical School, the Partners HealthCare Center for Personalized Genetic Medicine, and Hewlett Packard, has been developing an integrated system for EHRs, clinical decision support (including tools for interpreting genetic tests), patient sample tracking, and research and clinical information database mining to find new correlations between genes and disease or treatment response.[54]

By the end of 2009, the system will be used by Massachusetts General Hospital to record the genetic fingerprints of nearly all of their cancer patients' tumors in an effort to make personalized medicine the standard of care.[55]

Consumer Genetics / Personal Genomics

If Healthcare IT is the backbone of the elements required to develop and deliver personalized medicine, then genetic testing and personal genomics perhaps represent the most recognizable face of personalized medicine for the average healthcare consumer today.

Genetic testing has been a part of medical practice for some time—but primarily under the direction of physicians and in limited applications such as screening for specific disorders and helping to determine or predict likelihood of response to treatment. Such tests have clearly led to improvements in outcomes and survival rates in a number of disease areas.

Within the past few years, a growing number of companies have begun to offer direct-to-consumer genetic tests, designed to help individuals better understand their genetic predisposition for certain health conditions. As supporting technologies have become less expensive, personal genomics companies have started to offer consumers whole genome scanning and associated information on individual genetic predisposition for a broad range of conditions simultaneously.

These new consumer products have spawned great interest and excitement, as well as concerns. For example, *TIME* magazine, in its November 10, 2008 issue, named "The Retail DNA Test" as number one among its "Best Inventions of 2008." Celebrities, entrepreneurs, and scientists alike have volunteered personal genetic information derived from scanning (and, more recently, sequencing), which

has further elevated the visibility of this field and, to some degree, personalized medicine more broadly.

Some critics have expressed concerns about the consistency and reliability of risk predictions, the clinical relevance of the testing results, the lack of regulation of testing companies, privacy, and even the ethics of providing information of this kind directly to consumers who may be unable to understand its significance.

It is clear, however, that consumer genetics and personal genomics offerings are becoming more a part of the mainstream, and they offer an opportunity for education and greater awareness of the role of genetics in helping to predict, treat, and even prevent the onset of disease. They may also eventually make a valuable contribution to research and discovery efforts, as some companies are beginning to develop initiatives to enable consumers to opt in to broad-based research initiatives.

> "When it comes to consumer genomics, expect the unexpected."
>
> **Ryan Phelan**
> Founder and
> Chief Executive Officer
> DNA Direct

POLICY, LEGISLATION, AND GOVERNMENT INITIATIVES

Personalized medicine is not pre-programmed for adoption into clinical practice. It requires changes in regulation, reimbursement policies, and legislative protections for privacy. The key parties involved in establishing a support system for personalized medicine—Congress, HHS [including the FDA and the Centers for Medicare & Medicaid Services (CMS)], and insurance companies—have taken note of the trend and have started to implement policies favorable to personalized medicine.

Regulation

The FDA has taken several steps to address the emerging practice of personalized medicine: by developing guidance for voluntary pharmacogenetic data submissions,[56] mitigating the threat that submitting such data might harm a product's pathway to regulatory approval; by publishing a draft guidance for pharmacogenetic and other genetic tests, including microarrays;[57] by publishing a concept paper for the co-development of pharmacogenomic drugs and diagnostics;[58] by permitting adaptive clinical trials that genetically enrich a study population as a trial proceeds in order to reduce the time required to establish safety and effectiveness;[59] by establishing labeling regulations (21 CFR 201.57) that recognize the relationship between genotype and drug response; and by establishing a precedent for microarray diagnostics regulation by approving the first such device for rapid genotyping of 29 CYP450 variants important for drug metabolism.[60]

The path to regulatory approval of new drugs and *in vitro* diagnostic tests is well established. In the United States, many tests developed and executed within academic and commercial labs are considered a service and are regulated by CMS under Clinical Laboratory [Improvement Amendments (CLIA)] rules.[61] Though not without controversy, the FDA has sought to regulate more complex tests such as those that profile multiple genes and require a mathematical algorithm to interpret (*in vitro* diagnostic multivariate index assays or IVDMIAs).[62]

To date, the list of diagnostic tests for personalized medicine approved by the FDA is short. (See Table 1 and **www.personalizedmedicinecoalition.org**) However, the number of pharmaceutical products with package inserts recommending a genetic test for prescription selection or dosage has grown substantially. There are now over 200 product labels that either recommend genetic testing or point to the influence of genetic variation on drug response or safety.[63] For example, the FDA recently updated the label for warfarin to recommend that a patient's genetic makeup be considered when deciding what dose to administer, bringing personalized medicine to one of the most widely prescribed drugs.[64]

Reimbursement

One of the most important factors influencing the integration of personalized medicine is the cost of the tests and treatments and whether public and private insurers will be willing to reimburse those costs. If Medicare and large insurers start routinely paying for genetic tests to guide the prescription of companion drugs, or to set out a plan for the prevention or management of chronic diseases, then personalized medicine will have reached a turning point. Beyond making next generation medicines

Milestones in Personalized Medicine

available to more people, reimbursement of personalized medicine products will set the stage for the collection of large amounts of real-world data, providing further support and demonstration of their benefits and cost savings.

Personalized medicine introduces a new way of thinking about disease, new technologies, and a greater emphasis on proactive and preventive medicine. This changed paradigm has presented several challenges for the reimbursement system. For predictive or preventive medicine, insurers have stated that they have little incentive to incorporate genetic tests because there is often such a high membership turnover rate that they cannot reap the long-term cost benefits of prevention that might result from genetic testing.[65] Tests are usually reimbursed only if the patient already exhibits signs or symptoms of disease.

The CMS rules for Medicare state that "tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute."[66] Such a policy will have to be modified to make full use of predictive screening tools offered by personalized medicine, including one-time tests (such as a CYP450 test for drug metabolism) that provide data on a host of conditions or pharmacogenomic effects relevant to the patient's entire lifetime of healthcare.

Even when a test can provide immediate benefits for selecting optimal treatment, avoiding dangerous side effects, or reducing the cost of overall care, current reimbursement policies have fallen short. Most payment rates for laboratory diagnostics have not been updated in 20 years, and new genetic tests are usually marked for reimbursement using outdated current procedural terminology (CPT) codes.

Furthermore, many of the services provided by genetics specialists required to help interpret the tests are not reimbursable, or they are undervalued under current payer policies. While the R&D costs for molecular diagnostics are significantly higher than those for conventional laboratory tests, due to extensive genomic research and clinical validation, Medicare generally does not recognize the high value-added aspect of the test when determining reimbursement levels.

There are indications, however, that the payment policies of both public and private insurers are beginning to move toward supporting personalized medicine:

- *The Advanced Laboratory Diagnostics Act of 2006* was introduced in Congress to reform Medicare reimbursement policies, in part to ensure that the payment system more accurately reflects the value of molecular diagnostic tests and their potential to reduce healthcare costs in the long run.
- *The American Association of Health Plans* has advocated a policy of encouraging genetic testing and preventive care, even for pre-symptomatic individuals when those tests can lead to improvements in care.[67]
- Several large private insurers, including Aetna, United Health, and Kaiser Permanente have instituted progressive coverage policies that pay for genetic tests identifying pre-symptomatic high-risk populations or that guide optimal therapy.

Payers have stressed that prognostic tests should be subjected to a rigorous assessment to determine their cost-effectiveness and impact on health outcomes in order to justify coverage. Several government efforts work to provide that critical mass of evidence. Sponsored by the Centers for Disease Control and Prevention (CDC), the *ACCE Project* is developing a model process for evaluating data on emerging genetic tests.[68] The project takes its name from the four components of evaluation—analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications. Building on the models developed by the ACCE, the *CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP)* project is collaborating with members of the insurance industry to support evaluation of genetic tests and other personalized medicine applications that are in transition from research to clinical practice and help establish standards for what constitutes adequate evidence for coverage.[69]

"The power in tailored therapeutics is for us to say more clearly to payers, providers, and patients,—'this drug is not for everyone, but it is for you'—that is exceedingly powerful."

John C. Lechleiter, Ph.D.
President and
Chief Executive Officer
Eli Lilly and Company

Legislation and Government Initiatives

Personalized medicine has become a priority healthcare issue at the highest levels of government. The enactment of a genetic privacy law, a department-wide initiative in HHS, and a bill introduced in Congress specifically for the support of personalized medicine, all attest to a groundswell of interest that has spurred decision-makers into action.

Passage of the *Genetic Information Non-Discrimination Act (GINA)* in 2008 was a landmark event for personalized medicine.[70] GINA ensures that all genetic information will be protected against misuse in health insurance and employment. The new law closed important gaps in the existing patchwork of federal and state protections. The fear of genetic discrimination leading to a loss of a job or insurance coverage (expressed by 68 percent of those surveyed[71]) has been a significant obstacle to full participation. By addressing this concern, and by securing a fundamental right to privacy, GINA clears the way for widespread use of genetic information in medical records and clinical decision making and will encourage the participation of patients in research linking genes to disease.

Recognizing that the government-sponsored Human Genome Project was a "race to the starting line," and that personalized medicine will now require changes in reimbursement policy, streamlined regulatory approvals, and infrastructure to support basic research and clinical care, HHS launched the *Personalized Health Care Initiative* to improve the safety, quality, and effectiveness of healthcare for every patient in the United States.[72]

Several reports have been published on the challenges facing personalized medicine and the actions required to prepare the ground for its future. The HHS *Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)* has released reports examining and recommending actions related to the integration of genetics into healthcare; the ethical, legal, and social implications of genomics in medicine; the medical education curriculum; and the impact of patent policy, privacy legislation, regulation, and insurance reimbursement.[73]

The *President's Council on Science and Technology* conducted a wide ranging review of the field and published its findings in the 2008 report *Priorities for Personalized Medicine,* making recommendations in eight major policy areas to the President and placing particular emphasis on supporting the development of technology and tools and modernizing regulation and reimbursement.[74]

The first congressional bill introduced to specifically encourage the development and adoption of personalized medicine was introduced by then Senator Barack Obama in 2006. The *Genomics and Personalized Medicine Act (GPMA)* acknowledged the potential of personalized medicine to improve the quality of healthcare and the policy changes needed to create a more accommodating landscape for it to thrive.[75]

July 2007
The FDA issues a *Draft Guidance for In Vitro Diagnostic Multivariate Index Assays.*[13]

August 2007
The FDA re-labels the blood thinning drug warfarin to recommend adjusting the dose based on genetic variation.

April 2008
James Watson's genome is sequenced in two months for $1,000,000.

May 2008
The Genetic Information Non-Discrimination Act (GINA) is signed into law.

The first high-resolution sequence map of human genetic variation is produced.

July 2008
The FDA recommends genetic testing before taking the HIV drug abacavir to reduce allergic reactions.

CLINICAL ADOPTION

A number of hospitals and regional healthcare systems have committed to putting personalized medicine into practice as early adopters. In addition to the institutions described earlier for their design and implementation of healthcare information systems, several organizations are notable for their clinical adoption of personalized medicine, including Baylor College of Medicine (BCM) Personalized Medicine Alliance; Cleveland Clinic Genomic Medicine Institute (CC GMI); Coriell Personalized Medicine Collaborative (CPMC); Duke University Institute for Genome Sciences & Policy (IGSP) and its Center for Genomic Medicine; Emory University and The Ohio State University Medical Center in the Alliance for Predictive and Personalized Health; Marshfield Clinic Personalized Medicine Research Program; Mayo Clinic Individualized Medicine Center; H. Lee Moffitt Cancer Center "Total Cancer Care"; Yale School of Medicine Boyer Center for Molecular Medicine; Ohio State University Center for Personalized Health Care; and Partners HealthCare Center for Personalized Genetic Medicine (PCPGM).

Clinical programs for personalized medicine also exist at Brown University; Children's Hospital Oakland Research Center; Children's Mercy Hospitals and Clinics; Cincinnati Children's Hospital Medical Center; El Camino Hospital; Georgetown University; George Washington University Medical Center; Hartford Hospital; Johns Hopkins Medical Center; Mount Sinai Hospital in New York; National Jewish Medical and Research Center; University of Pennsylvania; University of Medicine and Dentistry of New Jersey Institute of Genomic Medicine; University of Chicago Institute for Genomics and Systems Biology; University of Utah; and Vanderbilt University.

The level of investment from these large hospitals and healthcare organizations will help extend the reach of personalized medicine into routine care, which enables us to end with a statement of context, rather than just a listing of centers.

Medical Education

Physicians and other healthcare providers will have to administer or advise on the application of growing numbers of molecular and genetic tests and pharmacogenomic drugs, make treatment decisions based on more predictive evidence and estimations of risk, utilize information systems for managing patient care, and deal with new ethical and legal issues that arise from molecular and genetic testing.

The majority of medical education institutions have not incorporated genetic or genomic courses into their curricula, leaving most healthcare workers unprepared for the next evolution of medicine.[76] Only a few comprehensive genomic education programs exist worldwide. These include programs at Tel Aviv University School of Medicine, the University of California San Francisco, and Duke University. Several medical schools have added clinical residencies to their updated curriculum that focus on the practice of genomic medicine, including Harvard Medical School, Cleveland Clinic Lerner College of Medicine, and Baylor College of Medicine.

Non-physician specialists, including nurses, pharmacists, and genetic counselors, will also play a more prominent role in providing care and advice to patients. The Genetic Nursing Credentialing Commission (GNCC) offers a certification program for practical and registered nurses seeking a specialty in genetics while the International Society of Nurses in Genetics (ISONG) established standards of practice for nurses specializing in genetics.
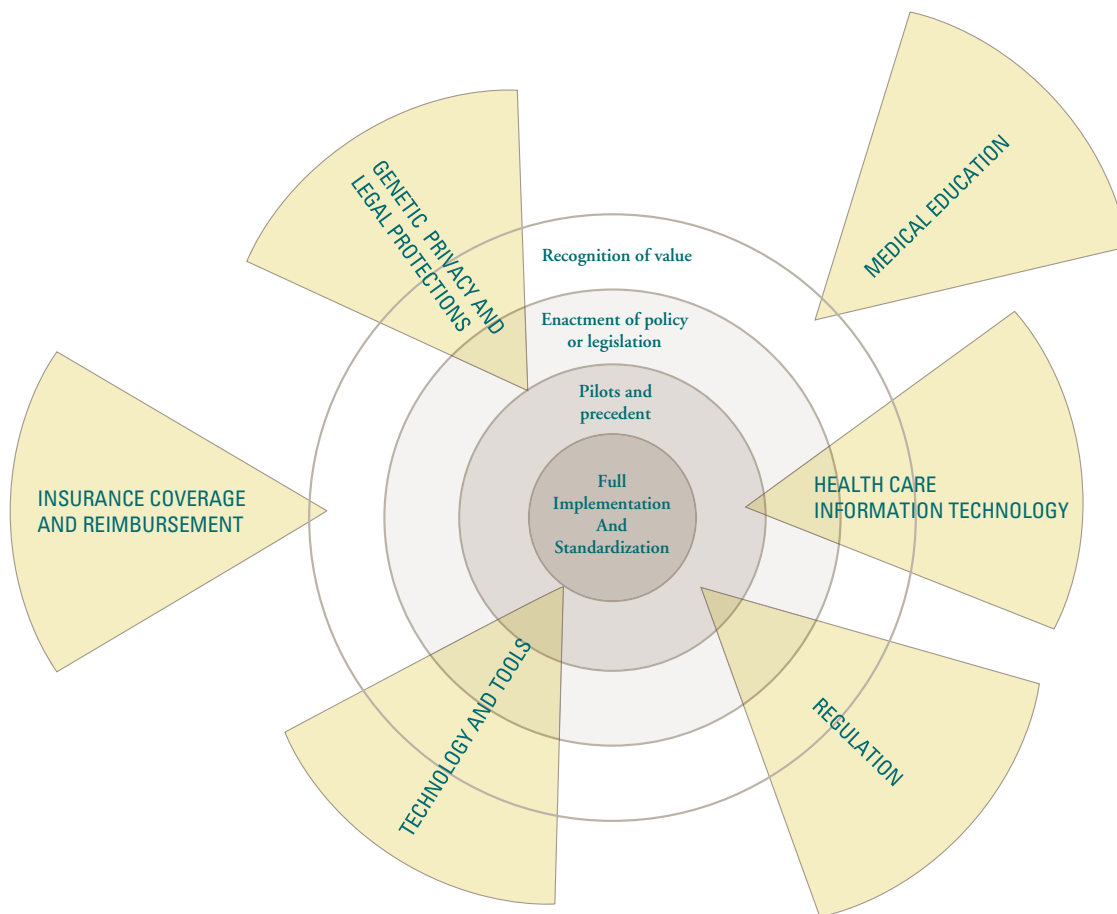
The National Coalition for Health Professional Education in Genetics (NCHPEG) is currently working with the American Academy of Family Physicians to develop a series of Web-based continuing medical education [(CME) programs on genetically] influenced health conditions, and it has developed a set of core competencies to help guide the development of educational initiatives in genetics across a wide range of medical professions.[77]

> "We have never been in a better position to advance cancer treatment… we know how to personalize therapy to the unique genetics of the tumor and the patient."
>
> *Richard L. Schilsky, M.D.*
> *Former President*
> *American Society of Clinical Oncology (ASCO)*
> *Professor of Medicine*
> *University of Chicago Medical Center*

CONVERGENCE OF FORCES

Figure 3: State of Personalized Medicine Adoption

- GENETIC PRIVACY AND LEGAL PROTECTIONS
- MEDICAL EDUCATION
- INSURANCE COVERAGE AND REIMBURSEMENT
- HEALTH CARE INFORMATION TECHNOLOGY
- TECHNOLOGY AND TOOLS
- REGULATION

Recognition of value

Enactment of policy or legislation

Pilots and precedent

Full Implementation And Standardization

The implementation of personalized medicine requires a confluence of several sectors (represented by wedges in the diagram). Concentric circles and range represent stages of implementation for each sector from public or stakeholder recognition of the value of personalized medicine, the establishment of supporting policies and laws, the launch and execution of smaller scale pilot programs and projects, to the final stage of full implementation and widespread use. Full implementation of personalized medicine can only be achieved when all sectors converge toward the center.

August 2008
Pharmacy benefits manager Medco collaborates with FDA to study the impact of genetic testing on the prescription of drugs and their effectiveness.

September 2008
The President's Council of Advisors on Science and Technology (PCAST) issues the report, *Priorities for Personalized Medicine.*[14]

October 2008
Ten prominent individuals release their genomic data as part of the Personal Genome Project.

March 2009
Massachusetts General Hospital announces plans to genotype every cancer patient to implement personalized medical care.

April 2009
Senate brings personalized medicine into national budget discussions.

"…We are in a new era of the life sciences, and the truth of that statement can be seen in fields from medical imaging, to new biologic drugs, and even to the use of DNA technology to improve our environment and reduce greenhouse gasses. But in no area of research is the promise greater than in the field of personalized medicine."

Senator Edward M. Kennedy (D – Mass.)
Remarks on the Senate's Consideration of the Genetic Information Nondiscrimination Act
April 24, 2008

The actions of healthcare organizations, industry, government institutions, Congress, and the two most recent Presidential administrations have recognized that personalized medicine requires an alignment of laws, regulatory and insurance reimbursement policies, healthcare information technology, medical education, and research investment. Each element of that infrastructure has progressed at a different pace, and certain areas, such as insurance reimbursement and medical education, will require a substantial effort to change mindsets and create new policies (Figure 3).

When all of the pieces of infrastructure fall into place; when we begin to classify and treat diseases not just by their most obvious signs and symptoms, but also by their molecular profiles; when physicians combine their knowledge and judgment with a network of linked databases that help them interpret and act upon a patient's genomic information; when insurance companies pay for tests and treatments that anticipate the needs of the patient as much as it reacts to them; and when regulators insist on using all information available to the physician, including genetic tests, to ensure the safety and efficacy of an approved drug, then "personalized medicine" will be known, simply, as medicine.

"If we are to achieve higher quality care for all Americans at a sustainable cost, we must look to those changes that improve the productivity of healthcare in the same way that we see quality gains traveling hand-in-hand with lower costs in other sectors throughout our economy. Personalized medicine seeks to use advances in knowledge about genetic factors and biological mechanisms of disease coupled with unique considerations of an individual's patient care needs to make healthcare more safe and effective. As a result of these contributions to improvement in the quality of care, personalized medicine represents a key strategy of healthcare reform. The potential application of this new knowledge, especially when supported through the use of health information technology in the patient care setting, presents the opportunity for transformational change.

Today, it is common for a medical product to be fully effective for only about 60 percent of those who use it. As the medical community is now learning, this in part reflects biological variation among individuals that affects the clinical response to medical interventions. In the past, they have not had the tools or knowledge to understand those differences. In the future, when doctors can truly prescribe the right treatment, to the right person, at the right time, we will have a new level of precision and effectiveness that will provide the knowledge-driven power that is necessary to achieve our highest goals in healthcare reform—including more effective disease prevention and early disease detection."

HHS Secretary Kathleen Sebelius

Written testimony given during Senate confirmation hearings, April 2, 2009

Table 1: Selected Personalized Medicine Drugs, Treatments, and Diagnostics as of March 2009*

Therapeutic product label contains pharmacogenomic information as:
- Information only
- Recommended
- Required

THERAPY	BIOMARKER/TEST	INDICATION
Herceptin® (trastuzumab) Tykerb® (lapatinib)	HER-2/neu receptor	**Breast cancer**: "…for the treatment of patients with metastatic breast cancer whose tumors over-express the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease."
Pharmaceutical and surgical prevention options and surveillance	BRCA 1,2	**Breast cancer**: Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer.
Tamoxifen	Aviara Breast Cancer Index℠ (HOXB13, IL17BR)	**Breast cancer**: Calculates a combined risk analysis for recurrence after tamoxifen treatment for ER-positive, node-negative breast cancer.
Chemotherapy	Mammostrat®	**Breast cancer**: Prognostic immunohistochemistry (IHC) test used for postmenopausal, node negative, estrogen receptor expressing breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy.
Chemotherapy	MammaPrint®	**Breast cancer**: Assesses risk of distant metastasis in a 70 gene expression profile.
Coumadin® (warfarin)	CYP2C9	**Cardiovascular disease**: "an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles."
Coumadin® (warfarin)	VKORC1	**Cardiovascular disease**: "Certain single nucleotide polymorphisms in the VKORC1 gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin."
Coumadin® (warfarin)	PGx Predict™: Warfarin	**Cardiovascular disease**: Determines CYP2C9 and VKORC1 genotypes to predict likelihood of adverse events with warfarin therapy.
Coumadin® (warfarin)	Protein C deficiencies	**Cardiovascular disease**: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has been associated with tissue necrosis following warfarin administration.
Pharmaceutical and lifestyle prevention options	Familion® 5-gene profile	**Cardiovascular disease**: Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Statins	PhyzioType SINM	**Cardiovascular disease**: Predicts risk of statin-induced neuro-myopathy, based on a patient's combinatorial genotype for 50 genes.
Atorvastatin	LDLR	**Cardiovascular disease**: "Doses should be individualized according to the recommended goal of therapy. Homozygous Familial Hypercholestremia (10-80mg/day)and heterozygous (10-20mg/day)."
Camptosar® (irinotecan)	UGTIA1	**Colon cancer**: "Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects."
Erbitux® (cetuximab) Gefitinib Vectibix® (panitumab)	EGFR expression	**Colon cancer**: "Patients enrolled in the clinical studies were required to have…evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit." EGFR positive individuals are more likely to respond to the drug than those with reduced EGFR expression.
Erbitux® (cetuximab) Gefitinib Vectibix® (panitumab)	KRAS	**Colon cancer**: Certain KRAS mutations lead to unresponsiveness to the drug.
Erbitux® (cetuximab) and Vectibix® (panitumab) Fluorouracil Camptosar® (irinotecan)	Target GI™	**Colon cancer**: Provides information of the expression of key molecular targets—KRAS, TS, and TOPO1—to guide therapy.
Tegretol (carbamazepine)	HLA-B*1502	**Epilepsy and bipolar disorder**: Serious dermatologic reactions are associated with the HLA-B*1502 allele in patients treated with carbamazepine. "Prior to initiating Tegretol therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present."
Immunosuppressive drugs	AlloMap® gene profile	**Heart transplantation**: Monitors patient's immune response to heart transplant to guide immunosuppressive therapy.
Ziagen® (abacavir)	HLA-B*5701	**HIV**: "Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended."
Selzentry® (maraviroc)	CCR5 receptor (1)	**HIV**: "Selzentry, in combination with other antiretroviral agents, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1 detectable…"

Budesonide	IBD Serology 7	**Inflammatory bowel disease**: Identifies subset of patients who will benefit from budesonide.
Gleevec® (imatinib mesylate)	*BCR-ABL*	**Leukemia**: "Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive [indicated by presence of *BCR-ABL*] chronic myeloid leukemia (CML) in chronic phase."
Dasatinib	Philadelphia Chromosome	**Leukemia**: "Dasatinib is indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy"
Busulfan	Philadelphia Chromosome	**Leukemia**: "Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph1) chromosome."
Purinethol® (mercaptopurine) Thioguanine Azathioprine	TPMT	**Leukemia**: Guides adjustment of dose in treatment of acute lymphoblastic leukemia: "Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe Purinethol toxicity from conventional doses…"
Tarceva® (erlotinib)	*EGFR* expression	**Lung cancer**: The test determines patients most likely to respond.
Capecitabine	DPD	**Multiple cancers**: "Rarely, unexpected severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity."
Pharmaceutical and surgical treatment options and surveillance	*MLH1, MSH2, MSH6*	**Multiple cancers**: Guides surveillance and preventive treatment based on susceptibility risk for colon and other cancers.
Chemotherapy	CupPrint™	**Multiple cancers**: Determines cancer classification for tumors of unknown primary origin.
Chemotherapy	Aviara CancerTYPE ID®	**Multiple cancers**: Classifies 39 tumor types from tumors of unknown primary origin, using a gene expression profile.
Elitek® (rasburicase)	G6PD deficiency	**Multiple cancers**: "Rasburicase administered to patients with glucose- phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. … It is recommended that patients at higher risk for G6PD deficiency … be screened prior to starting ELITEK therapy."
Drugs metabolized by CYP P450 **2C19**: Celecoxib, Codeine, Diazepam, Esomeprazole, Nelfinavir, Omeprazole, Pantoprazole, Rabeprazole, Voriconazole **2D6**: Acetaminophen, Aripiprazole, Atomoxetine, Carvedilol, Cevimeline hydrochloride, Clozapine, Fluoxetine HCl, Fluoxetine HCL and Olanzapine, Metoprolol, Propranolol, Propafenone, Protriptyline HCl, Risperidone, Tamoxifen, Terbinafine, Thioridazine, Timolol maleate, Tiotropium bromide inhalation, Tolterodine, Tramadol, Venlafaxine	Amplichip® *CYP2D6/CYP2C19*	**Multiple diseases**: FDA classification 21 CFR 862.3360: "This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information."
Rifampin Isoniazid Pyrazinamide	NAT	**Multiple diseases**: N-acetyltransferase slow and fast acetylators and toxicity- "slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions."
Rituximab	PGx Predict™: Rituximab	**Non-Hodgkin's lymphoma**: Detects CD-20 variant (polymorphism in the IgG Fc receptor gene *FcgRIIIa*) to predict response to cancer drug rituximab.
Celebrex® (celecoxib)	*CYP2C9*	**Pain**: "Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance."
Risperdal® (resperidone) Zyprexa® (olanzapine)	PhyzioType PIMS	**Psychiatric disorders**: Predicts risk of psychotropic-induced metabolic syndrome, based on a patient's combinatorial genotype for 50 genes.
Gleevec® (imatinib mesylate)	*c-KIT*	**Stomach cancer**: "Gleevec® is also indicated for the treatment of patients with Kit (*CD117*) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)."

*This list is not intended to be comprehensive but reflects commonly used or available products as of March 2009. Some products, for which the FDA recommends or requires pharmacogenomic testing or which have pharmacogenomic information in their label, are listed at the FDA's Web site (http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm). Other listed products that are novel, and/or that address large populations, have been identified via websites and public announcements.

Indications in quotes are taken from the therapeutic product label.

BCR-ABL = breakpoint cluster region – Abelson	DPD = dihydropyrimidine dehydrogenase	TOPO1 = topoisomerase 1
BRCA 1,2 = breast cancer susceptibility gene 1 or 2	G6PD = glucose 6 phosphate dehydrogenase	TPMT = thiopurine S-methyltransferase
c-KIT = tyrosine kinase receptor	HER2 = human epidermal growth factor receptor 2	TS = thymidylate synthase
CYP = cytochrome P450 enzyme	NAT = N-acetyltransferase	*UGT1A1* = UDP-glucuronosyltransferase 1A1

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