

A Submission to The National Institute of Standards and Technology's (NIST) Technology Innovation Program (TIP)

CRITICAL NATIONAL NEED IDEA:

Advance Personalized Medicine to Transform the U.S. Healthcare System

Submitting Organization: **The Personalized Medicine Coalition**
The Personalized Medicine Coalition, representing a broad spectrum of academic, industrial, patient, provider, and payer communities, seeks to advance the understanding and adoption of personalized medicine for the benefit of patients.

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Submitted: December 1, 2008

Why NIST's TIP Should Focus on Personalized Medicine:

1. Our nation's healthcare system faces unprecedented challenges and is clearly a critical need that must be addressed through public-private sector collaboration. It is among the highest areas of cost employers and our government face—in excess of \$2 trillion annually, and growing. Millions of patients and families experience the impact of its inadequacies daily and eagerly await new innovations that could transform the system and deliver vastly superior results—*results that would accompany the further advancement and adoption of personalized medicine.*
2. Personalized medicine offers the potential to transform our healthcare system by enabling an individualized approach to care based on an advanced understanding of the molecular underpinnings of disease and the unique biology of each individual. At its most basic level, it can enable providers to assure the right treatment for the right individual at the right time—and thus dramatically improve health outcomes. Writ large, it offers the potential to help individuals to avoid the onset of disease and to manage their health much more effectively throughout their lives. *Although the continued advancement of personalized medicine requires significant up front investment in research and development, the potential return to society will be significant, sustained, and measurable.*
3. The failure to capture the full potential of personalized medicine, on the other hand, could have significant long-term and potentially catastrophic impacts on the U.S. healthcare system, millions of patients, as well as our economy and global competitiveness. Close to a third of all investment in healthcare today goes toward interventions or other measures that do nothing to improve health outcomes. If we continue to invest in a system that fails patients a third of the time—and recognizing that aging “boomers” are projected to significantly elevate demands on our system—we are in essence just buying more shovels to dig a deeper hole. *Alternatively, if we increase our investment in genomic, proteomic, and other research that has been shown to yield significant breakthroughs, and in the systems needed to support the development and application of these breakthroughs in patient care, we will reverse the course of healthcare demand in this country and significantly increase the effectiveness and efficiency of care.*

The Personalized Medicine Coalition, representing a broad spectrum of academic, industrial, patient, provider, and payer communities, asks NIST to consider the development of initiatives under TIP that would support investment in high-risk, high-reward research. Such investments could have a significant impact on the advancement of personalized medicine in the U.S. and serve to accelerate progress toward a major and much needed transformation of our nation's healthcare system.

Introduction

Personalized medicine is an emerging field that many experts, and leaders in government, believe holds significant promise for improving medicine and potentially transforming the U.S. healthcare system.¹

Personalized medicine uses new methods of molecular analysis to better understand and manage a patient's disease or to assess that patient's predisposition toward a disease or response to treatment. The field includes genetic tests and other types of diagnostics, as well as targeted therapies. It helps providers and patients achieve optimal health outcomes by preventing or intervening early in the onset of disease and by identifying the approaches to treatment and care that are best for each individual.

It is increasingly evident that better understanding a patient's individual genetic and biochemical profile allows physicians to provide safer and more effective care. Reaching a point where such understanding is readily available to clinicians and patients will require significant additional investment in research and technology to pinpoint the molecular underpinnings of disease and to develop the diagnostics, tools, therapies, and information systems needed to truly deliver personalized healthcare.

The stakes for the successful development and adoption of personalized medicine approaches are exceptionally high, from both a health and an economic perspective. Tens of millions of Americans suffering from diseases for which personalized medicine-based diagnostics and treatments could be applied are eagerly awaiting progress in the field. Many, particularly those with particularly complex or relatively rare conditions, could be waiting a long time, as the bulk of the effort and available capital in the near term goes toward diseases that impact hundreds of thousands or millions of Americans. In some areas, such as neurology, where basic research is still needed to better understand both the function of the brain and the mechanisms of disease, the wait could be even longer.

Further adding to the urgency to accelerate advancement of personalized medicine is the burgeoning cost of healthcare, which is projected to continue to increase as our nation's "boomers" age. We already spend more than \$2 trillion annually on healthcare in U.S., and national health spending as a percentage of gross domestic product is projected to hit 20 percent by 2016.² Of that, the Congressional Budget Office estimates that about \$700 billion is invested in interventions that *do nothing to improve health outcomes*. Personalized medicine could have a huge impact on reducing wasted investment and poor outcomes, as it is all about finding the right treatment for the right patient at the right time. Costs could be reduced even further by the potential for personalized medicine to help individuals avoid the onset of disease altogether, or eliminate unnecessary procedures or catastrophic health events that can result from incomplete or improper diagnosis or treatment.

Additional investment is needed to advance the science behind personalized medicine and accelerate its development, adoption, and availability. We urge NIST to consider including personalized medicine under TIP as an area of critical national need—whereby funding of high-risk, high-reward research would not only serve to accelerate innovation, but also would help to transform the healthcare system to the benefit of all Americans.

¹“Personalized Health Care: Opportunities, Pathways, Resources.” U.S. Department of Health and Human Services. <http://www.hhs.gov/myhealthcare/news/personalized-healthcare-9-2007.html>. March 23, 2007.

² Poisal JA et al. Health Spending Projections Through 2016: Modest Changes Obscure Part D's Impact. *Health Affairs*. 21 February 2007;W242-253. Via “Health Insurance Costs.” National Coalition on Health Care. <http://www.nhc.org/facts/cost.shtml>. Accessed October 21, 2008.

The Basics

A major first step in developing a targeted, more “personalized” medicine is to find a “biomarker” that reflects some specific health state, such as aggressive tumor biology versus non-aggressive. A biomarker can also indicate if a patient is more or less likely to respond to a certain type of drug, thereby helping doctors match patients more quickly to promising treatments. Alternatively, a biomarker may predict which patients are particularly prone to side effects from certain classes of drugs, helping doctors avoid prescribing drugs that will harm or even cause fatal reactions in patients.

A biomarker is anything measurable, such as bone loss or a rise in white blood cells, but research is increasingly focused on genomic biomarkers because of the massive amounts of data and subsequent knowledge gleaned from the sequencing of the human genome—and massive gaps in knowledge still remaining to be filled. A small but growing number of genetic variations are thus being linked to common diseases such as diabetes, asthma, and arthritis. Even with this relatively recent progress, we have only begun to scratch the surface in terms of our understanding of the genetic linkages to disease—or, perhaps as importantly, the combined impact of genetics and environment in the development of disease.

Genes work by creating proteins, via the intermediate step of “gene expression,” where the gene’s “message” is encoded into molecules called RNA. Scientists have increasingly better tools to study the levels of RNA in the cell. They can also measure and identify both the proteins that result from the RNA message and the metabolites formed when proteins are broken down and other cellular processes occur. Gene expression, proteomic, and metabolomic studies are also notably on the rise, though these are less mature fields than genetic variation.

One of the things that made the early days of personalized medicine particularly challenging is that it linked two different kinds of products—diagnostics and pharmaceuticals—in a new way. Once researchers located a good marker of response, they could develop it into a diagnostic test. This link differed from the traditional drug development pathway and required additional and alternative resources and collaborations.

A recent review found that at least 121 current drugs on the market bear labels that mention genomic biomarkers: 69 of those biomarkers were human, the rest related to viruses or bacteria (Frueh et al. 2008).³ This development reflects the fact that our understanding of the genetic underpinnings of disease is growing exponentially and changing in critical ways. Looked at against the backdrop of all human disease, it also indicates just how far we still have to go.

³ Frueh FW et al., Pharmacogenomic biomarker information in drug labels approved by the United State Food and Drug Administration: Prevalence of related drug use. *Pharmacotherapy* 2008; 28(8):992-8.

Potential Benefits of Personalized Medicine

Personalized medicine affects medical practice, drug discovery and development, diagnostic development, and the healthcare system. Among the potential benefits are:

1. *Earlier disease detection:* Doctors will be able to diagnose disease much more quickly, which will mean more patients get better, faster. Doctors will also be able to test for many more conditions before symptoms have developed. Tests that indicate a predisposition to certain cancers and diseases are already available and have quickly become part of modern medicine. In the future, new tests will help provide treatment for people who only have warning signs of a disease, such as high cholesterol, or even before they develop any warning signs at all. The ability to interpret early indicators will shift medicine from a “reactive” to a “preventive” paradigm.
2. *Optimal therapy selection:* Instead of wasting months taking drugs that are not working while their disease progresses or facing painful, debilitating, or life-threatening side effects, patients will be quickly matched to the right drug for their condition.
3. *Fewer adverse drug reactions:* Our current system is based largely on a “trial and error” approach, with patients often experiencing serious side effects before they are eventually prescribed a drug that works for them. A growing number of genetic subtypes, however, have been linked to certain adverse drug reactions. Many costly and harmful drug side effects could be prevented by expanding this type of research and by making the results available and actionable via diagnostic tests and computerized treatment algorithms, which automatically report which medicines should be used and which should be avoided, based on genetic testing results.
4. *Better patient compliance with therapy:* Many patients do not even take the drugs that are prescribed for them. This problem is more common when patients cannot tell if a drug is actually working. The ability to confirm that a patient is receiving a drug that will truly benefit them should give patients greater confidence in the treatment and help keep more people on their prescribed medications.
5. *New and better targets for pharmaceutical and biotechnology drug development:* Finding specific molecular defects, such as HER2—the target for the highly successful breast cancer drug Herceptin®—can help pharmaceutical and biotechnology developers hone in on the key factors in a disease. That, in turn, would mean they will spend less money chasing dead ends and can better understand what drug interventions will affect the progression of disease.
6. *Faster, less expensive, and better drug trials:* Many drugs are never approved, despite very promising early results, because they cannot demonstrate efficacy in a large enough number of people. Herceptin®, for example, would not have been approved for breast cancer in the general population, because only about 25 percent of tumors respond to the drug. As a result, the drug did very poorly in studies that included women who were HER2 negative. If drug makers can use molecular tests to select patients for their trials who are most likely to respond to the drug being evaluated, they can more quickly ascertain if a drug works the way that it is supposed to. Patients who have no chance of responding to the drug are excluded from the early trials, and that makes it much easier to evaluate the drug’s true effectiveness. It also means that the drug will not be approved in the broader population and will not be given to patients with no chance of responding.

7. *The ability to use a wider range of drugs:* Once doctors can easily identify patients who should not take a drug, either because it will not work or because it might harm them, they can use a wider range of drugs. Many drugs that were not approved for the general population could have been approved if they were tested in the right patients, as Herceptin® eventually was. Drugs that have been removed from the market because they cause side effects in some patients might also be re-launched if there was a “companion test” that would help patients determine if the drug was going to harm them, allowing them to avoid taking the drug in the first place. The key to taking advantage of this expanded choice of drugs is the important and increasingly inextricable link between a drug and its matching companion diagnostic—a test that helps guide use of the drug.
8. *Fewer withdrawals of marketed drugs:* Often drugs seem to work well in clinical trials, but unacceptable side effects emerge when the drug is released to the general population and much larger numbers of people are taking it. Between 1995 and 2005, at least 34 drugs were withdrawn from the market (Need AC, et al. 2005).⁴ Scientists suspect that some hard-to-detect adverse effects from withdrawn drugs are related to individual genetic makeup. As the understanding of the underlying genetics of ADRs expands, drug makers will be able to predict more ADRs and provide tests that will guide prescriptions and preclude inappropriate patients from receiving them.
9. *A reduction in overall healthcare costs:* Over time, the promise of personalized medicine is that fewer unnecessary or inappropriate interventions will occur, fewer adverse reactions will result, and more preventive medicine will be practiced, reducing overall healthcare costs. Personalized medicine streamlines medicine, removing the inefficiencies inherent in the “one size fits all” paradigm.

Constituent and Political Interest in Personalized Medicine

Personalized medicine is starting to attract high-level attention from legislators and others involved in public policy. These policymakers demonstrated their understanding of and commitment to advancing personalized medicine by passing the Genetic Information Nondiscrimination Act (GINA) in 2008. This landmark legislation will ensure that all genetic information will be protected against misuse in health insurance and employment.

The recognition of the potential of personalized medicine is also spreading. In September 2008, the President’s Council of Advisors on Science and Technology (PCAST) released “Priorities for Personalized Medicine,” an objective look at the field that maps the barriers preventing its widespread adoption.⁵ “*The convergence of scientific opportunity and public health need represented by personalized medicine warrants significant public and private sector action to realize the development of a promising new class of new medical products,*” wrote John H. Marburger III, director of the White House Office of Science and Technology Policy, and E. Floyd Kvamme, co-chair of PCAST in a letter accompanying the report. Notably, PCAST comprises leading private sector, university, and other officials who counsel the president on science policy.

Former Senator and now president-elect Barack Obama introduced the Genomics and Personalized Medicine Act of 2007(S.976), a bill that aims to hasten the introduction of personalized medicine. This bill would improve and help coordinate public and private efforts to facilitate the development of safer and more effective drugs, create a biobanking initiative, expand the genomics workforce, improve the quality of clinical genetic testing, and more.

⁴ Need AC, et al. Priorities and standards in pharmacogenetic research. *Nat Genet* 2005; 37:671-681.

⁵ President’s Council of Advisors on Science and Technology. “Priorities for Personalized Medicine.” Sept. 2008.

In 2008, Representative Patrick Kennedy (D-RI) introduced an updated version of that bill, tagged H.R.6498. The new bill adds tax and credit incentives for researchers in this field.⁶ Kennedy's uncle, longtime Massachusetts Democratic Senator Edward Kennedy, also has expressed an interest in the field. Senator Kennedy sponsored a bill that would strengthen oversight of genetic and pharmacogenomic tests and encourage pharmaceutical companies and device makers to develop companion diagnostics.

U.S. House Speaker Nancy Pelosi has mentioned her support for personalized medicine during numerous public events. Pelosi applauded the signing into law of GINA in May 2008 and while speaking at a breast cancer awareness event said, "With the next great advancements in personalized medicine, we can ensure that every breast cancer patient receives the treatment that is tailored to her physiology and offers the best chance of success."⁷

Members of the George W. Bush administration have also taken steps to advance personalized medicine. In March 2007 Health and Human Services (HHS) Secretary Michael O. Leavitt announced policies, investments, and next steps for the HHS Personalized Health Care Initiative. Identified as a top HHS priority, the Initiative aims to improve the safety, quality, and effectiveness of healthcare by using information about genes and how they relate to drug treatment. According to the department Web site, this Initiative provides federal leadership supporting personalized medicine-related research and create a "network of networks" to collect anonymous health data that can be used to establish patterns and to identify gene/disease links.

Policymakers from both leading parties support personalized medicine. They understand that the country's financial challenges will only worsen if healthcare costs continue rising. These lawmakers also recognize that personalized medicine brings better quality of care as well as efficiency.

Early Clinical Applications

Personalized medicine has made its first, and so far most dramatic, impact in oncology. But the successes here have helped to inspire and inform efforts in other fields, where much new research is now also being carried out. Many people have heard of Herceptin® and Gleevec®, which are often described as personalized medicine's first big wins. These drugs have been joined by several other targeted therapies, but they still help to define the field.

It is notable that both Herceptin® and Gleevec® are biological drugs, which tend to come with higher pricing than conventional chemical entities. But both these drugs are so effective they can save on overall costs (McKeage K and Lyseng-Williamson KA 2008. Mabasa V et al. 2008).^{8,9} In addition, newer Herceptin®-like (e.g., Tykerb® [lapatinib]) and Gleevec®-like drugs have followed that offer advantages to particular types of patients, such as those who have developed resistance to the earlier drugs (Paul B et al. 2008).¹⁰ This

⁶ Rep. Kennedy revives Obama's Personalized Medicine Bill for next Congress; Adds incentives. *GenomeWeb News*, Sep. 10, 2008.

⁷ Press release: Pelosi Statement on National Breast Cancer Awareness month, Oct 2, 2007. <http://speaker.house.gov/newsroom/pressreleases?id=0352>

⁸ Mabasa VH et al. Verification of imatinib cost-effectiveness in advanced gastrointestinal stromal tumor in British Columbia (Vince-BC study). *J Oncol Pharm Pract.* 2008 Sep; 14(3):105-12.

⁹ McKeage K, and Lyseng-Williamson KA. Trastuzumab: a pharmacoeconomic review of its use in early breast cancer. *Pharmacoeconomics.* 2008; 26(8):699-719.

¹⁰ Paul B, Trovato JA, and Thompson J. Lapatinib: a dual tyrosine kinase inhibitor for metastatic breast cancer. *Am J Health Syst Pharm* 2008 Sep15; 65(18)1703-10.

ability to classify patients into increasingly specific categories marks a crucial transition for breast cancer therapy; doctors are moving from having limited choices to where they can consider a range of treatment options according to the characteristics of the patient's disease.

Infectious diseases like AIDS are another arena where the rewards from understanding the molecular basis of a condition have been seen early. Today, doctors can use tests to select those drugs that are most likely to control particular HIV strains (U.S. Department of Veteran Affairs HIF/AIDS Program literature).¹¹ They can also measure the levels of virus in the patient's bloodstream. This detailed and regular testing extends lives by matching patients quickly with the most effective drugs.

It is difficult to find a field of medicine where researchers are not performing genomic studies. For example, research into genetic variation has found links between genes and atrial fibrillation, autoimmune disease, bipolar disorder, colorectal cancer, type 1 and 2 diabetes, heart failure, hypertension, multiple sclerosis, restless leg syndrome, rheumatoid arthritis, and many other conditions.

Drugs that have not been effective enough in the general population to gain approval are also being "resurrected." Bucindolol, an experimental beta blocker for heart failure, was set aside in 2001 when it showed disappointing efficacy in a large Phase III clinical trial. However, that trial was unusual for the time in that it collected DNA samples from patients. The drug was bought by a new company, whose researchers looked at genetic data and found that patients with a specific genetic profile did noticeably better than other patients when taking the drug.¹² That genetic variation occurs in about half of all people. A test was developed that detects the variation, and the company has filed an application to market the drug, which would become the first cardiac drug to be prescribed based on a gene test.

What is Needed to Support the Continued Advancement of Personalized Medicine

The pharmaceutical industry has embraced biomarker discovery, and it routinely looks at markers for virtually every compound in development (Allison, May 2008).¹³ But coupling drugs to diagnostics is a new paradigm, which requires new strategies and partnerships. And while genotyping, used to find genetic variations, has matured rapidly, gene expression, proteomics, and metabolomics technologies still need considerable development.¹⁴

Another key development is that the industry has recognized that some projects are too big and complex to be done alone, and it is establishing public-private collaborations such as the Serious Adverse Event Consortium to address these more challenging areas. Most important is the need to develop information technology infrastructures capable of handling the massive amounts of genomic data being generated and integrating that with data available from public and proprietary sources.

As science progresses, gene, protein, and metabolite expression profiling are all coming of age as researchers improve their methods for picking out the crucial markers from an ocean of signals. Part of the difficulty with these particular studies is that they involve so many data points. As noted earlier, human DNA comprises 3 billion bases, which are expressed

¹¹ The United States Department of Veteran Affairs' National HIV/AIDS Program, "Genotypic Testing for HIV-1 Drug Resistance." 2004, April.

¹² Liggett SB, et al. A polymorphism within a conserved beta (1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Nat Acad Sci USA*. 30: 11288-93.

¹³ Allison M, Is personalized medicine finally arriving? *Nature Biotech*. May 2008; 26:509-517.

¹⁴ Service, RF, Will Biomarkers Take Off at Last? *Science*, Sept. 26, 2008; 321:1760-

as many different RNAs and then in many proteins. The number of RNAs, proteins, and metabolites is thus exponentially larger than the number of mutations in DNA. Gene expression, protein, and metabolomic markers often involve more than one data point and can involve hundreds. The sheer complexity and vertiginous amount of data that researchers must analyze requires sophisticated statistics and bioinformatics (the science of informatics as applied to biological research). Experts agree that this field is evolving rapidly, but major hurdles still remain, and it will likely require even more advances before this challenge is solved.

The ultimate goal for molecular biologists is not just to identify the genes, RNA, proteins, and metabolites important in disease but also to know how these work together in pathways or networks. Fully understanding these networks will require substantive investment and better bioinformatics tools than are currently available.

Other advances in medicine are also working in concert with the new molecular biology. For example, imaging instruments like positron emission tomography can be used with molecular tags to reveal biological processes in cells (Czernin J et al. 2006).¹⁵ This combined approach is leading to entirely new types of tests. Scientists can now “watch” processes such as gene expression, signal transduction, tumor cell metabolism, proliferation, apoptosis, hypoxia, and angiogenesis unfold. Tools like these are helping to speed drug research by letting scientists know much earlier, and with greater certainty, whether a targeted therapy works the way in which it was intended.

The early successes with molecular imaging have led to an explosion of research and rapid growth in the number of molecules available as “tags” for use with new imaging instruments. As these molecules are tested and validated, scientists will be able to view many more physiological and biological processes.

The ultimate goal is to have a portfolio of tests for each disease from which researchers can quickly, efficiently, and confidently perform simple tests based on those markers and take rapid action based on what the tests reveal.

¹⁵ Czernin J et al. Molecular imaging in the development of cancer therapeutics. *Annual Review of Medicine* 2006; 57:99-118.

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