WHITE PAPER

PRECISION MEDICINE

HOW CLOSE ARE WE TO ACHIEVING CLINICAL QUALITY AND VALUE?
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MOVING FROM RESEARCH TO STANDARD OF CARE

Each year, 1.6 million people in the United States are diagnosed with cancer. What if each one could get precisely targeted treatment based on detailed analysis of the patient’s specific genome, medical history, lifestyle, and environmental factors? What if personalized care could help patients reduce their risk of cancer in the first place? What if it could improve the prevention and treatment of chronic diseases, which consume as much as 80% of U.S. healthcare dollars?

This is the tremendous promise of precision medicine.

Improving outcomes

Precision medicine, which seeks to take each patient’s variability in genes, environment, and lifestyle into account in the prevention, diagnosis, and treatment of disease, is already improving patient outcomes:

• A 26-hour rapid whole genome sequencing method developed by Children’s Mercy Kansas City is helping to diagnose critically ill newborns. Timely sequencing of an infant's genome can help improve time to diagnosis and better determine the appropriate therapeutic response.

• “The importance of genomic profiling in the diagnosis and treatment of pediatric brain cancers is reflected in the World Health Organization’s recent decision to classify such tumors by the genetic alterations within them, rather than by broad tumor type,” according to Susan Chi, MD, co-senior author of a study on the value of genetic testing to improve diagnosis and treatment options for pediatric brain cancers at Dana Farber and the Boston Children’s Cancer and Blood Disorders Center. "Our findings show that precision medicine for pediatric brain tumors can now be a reality.”

• Researchers at the University of California San Diego School of Medicine found that cancer patients who were treated based upon individual genetics and biomarkers experienced a nearly 30% increase in positive response to treatment. They also had an increased rate of prolonged remission compared to patients in a traditionally treated group.

Genomic, molecular, and pharmacogenomic tools are providing insight into the variability of diseases other than cancers, including Alzheimer’s, autism, neurodegenerative diseases, and chronic conditions, such as diabetes.

• For the more than 20 million Americans with chronic kidney disease, researchers have identified an easily detectable protein in urine that distinguishes individuals at high risk for kidney failure requiring dialysis or transplant from those likely to maintain stable kidney function for years with minimal treatment.

• Biomarkers enable researchers to select trial subjects with specific characteristics for COPD studies to reduce the costs and time frames of clinical research.

• New point-of-care diagnostics are personalizing care at the bedside. The University of Pittsburgh Medical Center uses a blood test to identify gene variants that can make certain blood thinners less effective. The University of Florida has cut complications from stent procedures by 50% by using a genetic test that identifies which patients will be unresponsive to the anti-clotting medicine clopidogrel.

Figure 1. Global efforts are underway to collect genomic, lifestyle, environmental, and social data from millions of patients.
WHEN WILL PRECISION MEDICINE BECOME THE STANDARD OF CARE?

Despite dramatic progress in precision medicine, benchside advances—from genomics to biomarkers to molecular analyses (proteomic, microbiomic, metabolomic)—are generally not being used clinically to personalize care.

Most notably, genetic sequencing to inform cancer diagnosis and target treatment has not yet been incorporated into clinical care for most cancers. Cancer patients looking for genetic insight instead are turning to academic medical centers and often paying thousands of dollars out of pocket for their tumors to be sequenced and to get advice on treatment options based on the results.

Nevertheless, powerful trends are converging that lead many to believe that the day when meaningful analysis of individual patient data becomes a routine part of clinical care is closer than it might appear. Citing increasing demand for personalized medicine, new technologies, and favorable government regulations and standards, Global Market Insights, Inc. estimates the precision medicine market to grow to USD $87.79 billion by 2023.17 Is it feasible therefore to think that precision medicine will become a routine part of clinical care in the next five years? Consider the costs should that not happen.

The costs of imprecision

Physicians have long noticed that patients who seem to have the same disease can respond very differently to the same treatment, making the traditional one-size-fits-all approach to medicine ill-fit and largely ineffectual.

A recent efficacy study of the top 10 revenue-generating drugs reveals that millions of people are taking medications every day that do not improve their conditions. For some drugs, such as statins, as few as 1 in 50 patients may benefit.18

A drug deemed effective ‘30% of the time,’ might actually be better understood as “100% effective for 30% of the people who possess certain genes or proteins,” notes Todd Stottlemeyer, CEO of the Center for Personalized Health.19

The challenge is to determine which are the 30% of patients who will benefit and then to develop effective, targeted treatments that work for the remaining 70%.

Meeting the challenge with more precise, data-driven, personalized prevention and targeted care could significantly reduce the severity and duration of illness, but experts also estimate that we can address up to 14% of clinical waste with better prevention or higher-quality initial care—thereby helping to reduce the estimated $1 trillion of wasteful spending in the annual U.S. healthcare budget.20

FAMILIAR ROADBLOCKS

Hurdles to applying the latest genomic and molecular insights and technologies in clinical decisions and care include lack of data and application interoperability, regulatory and reimbursement constraints, legacy medical and IT technologies, institutional processes and procedures, and the natural conservatism of the medical community.

Data

Collecting data, managing data, sharing data, keeping data private and secure—it’s clear that data is at the heart of what makes precision medicine work—or not. Namely, the challenges of data management include:

- **Volume of data**: The more individual health data available for analysis, the greater the likelihood is of identifying genetic and molecular variants and delivering clinically relevant guidance to physicians and patients. Of the approximately three billion characteristics in the genomic code, some three million variants are specific to each individual—and genomic data is just part of a patient’s potential profile. Other data sources include electronic health records; medical tests (e.g., imaging, EKG, blood/urine analyses); medical device monitoring; social networks; and lifestyle, environmental, and socioeconomic factors. By 2025, genomic data is anticipated to grow by more than 2 exabytes (or 2 million terabytes) every year.21 Storing, analyzing, sharing, protecting, and scaling to handle such large volumes of data require new technologies and approaches.

- **Variety of data**: Adding to the challenge is the highly variable nature of data generated in healthcare—EHR applications, insurance claim forms, imaging, device streaming, genomic sequencing, and radiology and pathology reports. It is critical to efficiently handle both structured data (traditional reports, applications, and databases) and unstructured data (PACS, IoT sensors, and photos).
• **Interoperability of data:** Silos, proprietary data formats, nonstandard medical terminology, security and privacy regulations—semantic data interoperability has long been the stumbling block to accessing, sharing, and applying data at the point of care. Much of the focus in healthcare and policy has been on achieving EHR interoperability. However, most EHR applications are not yet equipped to store genomic data or the real-time data streaming from monitoring devices. Indeed, an application-centric approach creates silos of data that require significant integration effort to work together, as well as complicating data integrity, protection, security, and privacy efforts.

**Clinical-decision support issues**

Physicians and care teams need more than raw data. Genomic test reports, delivered in a read-only PDF document, are not sufficient for primary-care practitioners who have neither the time nor expertise to interpret them. They need clinically actionable datasets integrated with rules for decision support—and decision support integrated into workflow at the point of care. “When you think about precision medicine, what you really want is an online shopping cart experience,” said Dave Dimond, Chief Technology Officer for Dell EMC Healthcare. “You want to see a box that says ‘researchers like me are looking into this’ or ‘patients like her have tried this therapy with these results.’ It’s about personalization, just like what the big retailers are doing.”

**Regulations and standards**

Government, industry, and institutional standards, regulations, and incentives can have unintended consequences that inhibit innovation. A major problem is their inability to keep pace with rapid innovation and progress. HIPAA, for example, was written in the era of desktop PCs and single-source data sets—when the benefits of data and sharing were not so recognized. Sadly, HIPAA-compliant patient records have proven vulnerable to security breaches and fraud, as indicated by the National Health Care Anti-Fraud Association (NHCAA) estimate of tens of billions of dollars lost to healthcare fraud each year. HITECH brought needed updates, but regulatory efforts continue to lag behind the rapid advances in precision medicine, as well as what new cloud-computing, security, and open source consensus approaches can bring to the table in terms of keeping data safe at rest and in transit and in developing meaningful standards that evolve.

**Reimbursement issues**

Insurers have been slow to provide coverage for precision medicine. In a recent survey, 11 major U.S. payers, covering more than 160 million patients, deemed genetic hereditary cancer panels (HCP) a “poor fit with coverage frameworks,” “experimental,” and having “insufficient evidence”—despite their potential to improve cancer-risk assessment. As evidence mounts for proactive and personalized care's reducing costs and improving outcomes, so will pressure on insurers to cover these services.

**PATIENTS ARE NOT WAITING**

Patients are perhaps the most powerful force in driving precision medicine forward and into clinical care. With the rise of the Internet, easily accessed health information, and social networking, patients have become evermore empowered, active participants in their own care.

**Patients are highly motivated and technically savvy**

Many cancer patients or patients with degenerative or chronic conditions are taking it upon themselves to learn as much as they can about their conditions. Some are even pushing for the latest treatments, including experimental ones. A growing percentage of cancer patients are demanding genetic personalization and precision in their diagnoses and treatments, often bringing direct-to-consumer lab-developed genetic tests (LDTs), analyses, and advice to their oncologists. Patients of all kinds are increasingly asking their doctors, "Is this treatment right for me?"

Public awareness of the role of genomics in cancer treatment is growing steadily, and with it, the request for genetic testing to inform treatment is becoming more commonplace. Companies like 23andMe have made genetic testing mainstream, with $199 direct-to-consumer tests that examine about 650,000 locations in a customer’s genome to produce reports on ancestry and health traits that “meet FDA standards for clinical and scientific validity.” After forcing 23andMe to take its initial health test off the market in 2013, the FDA now allows the company to sell genetic tests...
direct to consumers for disease risk, including cystic fibrosis, Alzheimer's, and Parkinson's.25

Beyond taking greater charge of their own care, patients are using social networking, open-source crowdsourcing techniques, and online crowdfunding to accelerate research into better diagnoses, treatments, and cures. These forums have enabled families with rare diseases to find each other and have provided platforms for advocates pushing for more research dollars to be spent on finding cures for less well-known medical disorders. Technically savvy diabetic patients have banded together, using the Twitter hashtag #WeAreNotWaiting26 as part of a multipronged effort to "stop waiting" for others to deliver the innovations they need and to make it happen themselves.

WHO OWNS, AND PROFITS FROM, PATIENT DATA?

Concern is growing among patients and others regarding their personal health data—who owns it, who has access to it, how will it be used, and who can profit from it.

Most patients and patient advocates believe that patients should "own" their medical data, control who has access to it, and be able to take it with them as they move from provider to provider. The goal of a single, shared, longitudinal patient medical record remains elusive. Patients continue to find a lack of coordination among multiple providers, realizing that it is up to them to make sure that their medical data is accurate and up-to-date in multiple locations.

So why do some providers put up barriers to patients being able to access their EHR? Reasons include:

- Regulatory requirements to maintain and preserve the master record
- Worries about lost or corrupted data, including intentional editing by patients to remove "embarrassing" but critical health information, "doctor shopping" for opioid prescriptions, etc.
- Frank but important doctors' notes about patients and their behaviors, etc.

These concerns could be addressed technically; for example, by providing patient access to read-only copies of their records, a controlled process for patients' updates and corrections, defined fields for MD notes that are stripped from patient versions, and so on.

One study, in which patients were given access to their EHRs, including doctors' notes, found that 92% of patients viewed their notes. Seventy-seven percent who did felt more in control of their care, and 99% wanted continued access. Many of the physicians who resisted the idea at first ended up changing their position.27

Another reason for limiting patients' access to their medical data is the concern that it is too complex for patients to understand or use. Recently, however, a team of researchers, medical professionals, software engineers, and patient advocates worked together to develop a report that enables cancer patients to read and understand the molecular analysis of their cancer so that they can make informed contributions to decisions on their treatment options.29

Two-way transparency and portability

The right balance seems to be one of two-way transparency in which both physicians and patients receive and review copies of the medical records, with the patients authorizing access. Emerging technologies, such as blockchain, might be used to control record integrity and grant access and authorization as needed. A decentralized encrypted technology developed to enable the Bitcoin digital currency, blockchain could be used to control access to health records using public and private keys, while maintaining a tamperproof, auditable record of care. Although the size of clinical data far exceeds blockchain's storage capabilities, the actual data could be stored "off the chain," with all authorized participants receiving a copy of all transactions and record history.30
Profiting from patient data

As the value of individual patient data in developing new therapies, services, and devices becomes more apparent, the question of who owns—and who profits from—patient data has taken a new turn.

Over the past decade, 23andMe has built the world’s largest genetic database, containing data from 1.2 million DNA samples, augmented by information provided by its customers through survey questions. The value of this patient health data can be gauged by the fact that a dozen companies have paid to gain access to subsets of this data, including Genentech, which paid USD $10 million to look at the genes of people with Parkinson’s disease.33

The proliferation of public, consortium, and private lab and corporate databases containing personal genetic and health information raises a number of questions. How is an individual’s privacy being protected? Are even HIPAA standards being applied? Should private enterprises have the right to profit from someone else’s personal health data? Or should there be a well-defined line in ownership rights between raw medical data, and proprietary tools, services, or discoveries made with that data? What roles might government and industry play in setting standards for anonymizing and keeping patient data safe from misuse? The Genetic Information Nondiscrimination Act (GINA) of 2008,34 for example, while protecting against genetic discrimination in employment and healthcare insurance coverage, does not protect against genetic discrimination by life, disability, or long-term care insurance companies.

TURNING DISRUPTION INTO OPPORTUNITY

Rapid advances in genome sequencing and molecular medicine are poised to have a disruptive impact on the healthcare system. The Medical Futurist, Dr. Bertalan Meskó, likens the impact of disruption to the discoveries of bacteria, viruses, and human blood-type groups. Accelerated progress can be seen in a number of areas:

- **Genome sequencing**: The reduction in both time and cost of sequencing is dramatic. It took 13 years and $3 billion to complete the first whole human genomic sequence in 2000. Today, a whole genome can be sequenced for about $1,000 in as little as 22 minutes.31,32 Within five years, the price for whole genomic sequencing is expected to fall to $100. In another decade, sequencing could be completed in 94 seconds and cost $1, enabling every newborn to begin life with a complete digital DNA profile.35

- **Pharmacogenomic mapping**: Inova Women’s Hospital already offers newborns a free optional pharmacogenomics (PGx) test as part of its standard neonatal package of care. Pharmacogenomics, which combines pharmacology with genomics to gain insight into how different individuals will respond to different medications, is used to generate a MediMap™. The map relates variants in seven genes with 21 medications to provide all babies and care providers with life-long guidance on medications—including which to use or avoid and dosage recommendations to improve efficacy and reduce potential side effects.36
- **RNA sequencing**: Building on the insights provided by DNA profiling, researchers at the Translational Genomics Research Institute (TGen) have developed a deeper genetic analysis that sequences RNA. RNA sequencing provides an even more precise look at how cells behave and how medicine can intervene with everything from cancer to deadly viruses such as Ebola and Zika.

- **Molecular assays**: A growing set of assays identify patient-unique characteristics at the molecular level, such as metabolites in the blood and microbes in their microbiomes. New devices are capable of identifying tumor DNA circulating in the bloodstream for much earlier, much less invasive testing and detection.

- **Optimized NGS sequencing appliances**: New, purpose-built genomics appliances combine optimized algorithms for multiple next-generation sequencing (NGS) pipelines with innovative high-performance computing (HPC), storage, and bandwidth technologies. Not only are the systems able to speed the analysis of vast quantities of diverse types of data more quickly—analyzing a whole human 30x genome in as little as 22 minutes—but they also replace expensive clusters of large servers with a single, easy-to-manage HPC appliance. By significantly reducing complexity and capital and operational costs, they enable more research in more places.

- **Cloud**: On-premises, public, and hybrid cloud platforms enable organizations to share computing and storage infrastructure and data. They also provide built-in security, data protection, and privacy and eliminate the need for data duplication at local sites. Where bandwidth is an issue, portable analysis workflows can be used to send an analysis to where the data is, rather than downloading the data locally for analysis.

- **Changing industry**: The rise of precision medicine is blurring the lines between research, life sciences, and care delivery, opening opportunities for innovation outside of the traditional healthcare structure. Large pharma and biotech companies are looking at more agile and efficient business models that will enable them to profitably develop and deliver smaller lots of customized therapies to smaller patient markets. New opportunities are arising just as the traditional approach to drug development is proving unsustainable, with the cost of developing a new prescription drug in the U.S. estimated at $2.6 billion.

- **Changing role of government**: Rapid technology developments are driving new approaches to government regulation and oversight. Agencies are driving multi-stakeholder processes to identify standards, define rules, and clarify technical and legal issues related to patient protection, privacy, and security. The FDA, for example, plans to use crowdsourcing to change the way genetic and other molecular diagnostics are developed, evaluated, and regulated.

### HERE TODAY: DATA LAKE-ENABLED HEALTHCARE ANALYTICS AS A SERVICE

In much the same way that advances in technology have unlocked genomics, new technologies are removing stubborn healthcare data interoperability and analytics roadblocks.

One significant breakthrough is the evolution of the "data lake" from concept to practical platform. Data lakes provide a single, scalable repository for constantly ingesting, aggregating, managing, filtering, analyzing, and interpreting vast volumes of data from both internal and external data sources. They aggregate all types of structured and unstructured data, so a single lake can contain reports, images, and real-time streaming data from medical devices and IoT sensors.

In addition to pooling all types of data, the data lake maintains data in its native format. Each data element is assigned its own standardized, unique identifier to enable semantic interoperability, while preserving the native data format underneath. As a result, researchers can link diverse types of data in new ad hoc ways and clinicians can use natural language queries to explore seemingly unrelated pieces of information. Metadata is used to provide data traceability, verification, governance, integrity, privacy, and security.

Partners® HealthCare is one of a number of healthcare providers using data-lake technology today. The large health system has built a single data repository, research workbench, and analytics environment to support precision medicine and Internet of Things (IoT) research to provide healthcare analytics as a service to its network of researchers and clinicians.

A variety of groups with different projects tap into the shared data-analytics platform as opposed to building their own back-end infrastructure from scratch and, in the process, creating another silo.

In addition to elastic, object-based storage capable of scaling to handle enormous datasets, the system serves up analytics sandboxes to analysts developing clinical decision support tools or researchers investigating clinical questions. Users manipulate data in their sandbox without affecting the availability or integrity of the data in the lake, which remains available to other researchers to use. As research is conducted,
results become part of the collective intelligence of the data lake. Partners HealthCare is already working on integrating new insights into clinical decision support, such as developing care guidelines and predicting length of stay from patient admission data.22

**HERE TODAY: PUTTING PRECISION MEDICINE INTO PRACTICE**

As the evidence for better outcomes from more personalized and precise medicine grows, many physicians are not waiting to put it into practice.

**Physicians too are highly motivated and technically savvy**

Duke University Medical Center, for one, has moved ahead to develop and implement a new model of clinical care to realize the promise of precision medicine available today. The center is applying the best available tools within the framework of a Personalized Health Plan (PHP) for each patient to move from reactive, sporadic treatment of episodic disease to a proactive, personalized, preventive program. The model combines clinical judgment and patient engagement with biomarkers, genomic analysis, proteomic and metabolomic analyses, drug metabolism tests, and companion diagnostics to inform initial risk assessments, identify disease, customize therapy, and monitor and refine treatment based on patient progress. Each patient’s Personalized Health Plan is “a living, adaptable document—available to all team members—continually revisited in person, by phone, and/or via patient portals and mobile applications.”

The Veterans Health Administration (VHA) has conducted its own PHP pilots at diverse clinical sites and found that the primary care doctors can adopt PHP in their practices and workflows. Now the VHA is further refining and integrating PHP as part of a larger effort to improve veterans’ health.39

**THE GENOME IS OUT OF THE BOTTLE**

Now that we know that we each have a unique genetic code that may predispose us to specific health issues and cause us to respond very differently to interventions and treatments, it’s hard knowledge to ignore, especially if we or loved ones become seriously ill.

“Diagnosing acutely ill babies is a race against the clock,” says Stephen Kingsmore, M.D., D.Sc., president and CEO of Rady Children’s Institute for Genomic Medicine, who holds the Guinness World Records Title for fastest genetic diagnosis. "Up to one-third of babies admitted to a neonatal intensive care unit in the United States have a genetic disease, and more than 20 percent of infant deaths are caused by genetic illnesses. Treatments are currently available for more than 500 genetic diseases; for about 70 of these, initiation of therapy in newborns can help prevent disabilities and life-threatening illnesses."40

Continuing to push to bring the benefits of precision medicine to 'All of Us'—not only to treat disease but also to proactively prevent disease—is the clear path forward.

The disruption—and opportunities—will continue. CRISPR-Cas9 and its ability to precisely edit genes is already being used on human cells in the lab.41 Neural networks and deep learning algorithms will analyze data at superhuman speeds. The day when caregivers are served up a highly visual, multilevel, longitudinal view of each patient’s data along with analyses and recommendations generated by a rich variety of constantly updated decision tools could be surprisingly near.

As leaders of the precision medicine Initiative put it, "With support from patients, research participants, researchers, providers, and private sector innovators, we can make precision medicine a reality."42
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