Barriers to Implementation of Precision Medicine for Cancer Treatment in the U.S. Healthcare System.

by Subha Madhavan Ph.D

Cancer is a complex disease caused by a combination of genetic factors and environmental and lifestyle influences. These manifest across a wide spectrum of symptoms, outcomes, and response to therapy. Precision medicine in oncology implements clinical screening and tissue molecular profiling to characterize the genetic makeup of the patient (i.e., germline DNA) and of the tumor (i.e., somatic mutations). This consequently enables the identification and validation of treatments to reduce side effects, and improve outcomes. For example, current treatment for a breast cancer patient who has estrogen receptor positive (ER) breast cancer will potentially include tamoxifen, a drug shown to be effective against early stage receptor-positive cancers. However, tamoxifen is metabolized by the polymorphic CYP2D6 enzyme; certain genetic variants in the CYP2D6 gene may result in reduced drug efficacy in patients carrying those variants. Therefore, the knowledge derived from both a patient’s phenotypic and molecular profile has the potential to support clinical decision-making by understanding the likely benefits and risks of a particular treatment.

The current standard of care for cancer relies upon the "one size fits all" approach to treatment, which is flawed for several reasons. Firstly, patients are often subjected to drugs with toxic side effects that provide no benefit. As a result, patients and other payers may end up incurring substantial costs on treatment with no improvement in health. Secondly, effective treatments may not be identified until later stages of the disease. Therefore, patients who have already progressed on the disease may not benefit from a promising treatment. In such scenarios, precision medicine has the ability to predict patient response to specific therapies based on molecular profiling and other techniques, thereby increasing treatment efficacy and reducing the burden of disease overall. These benefits extend not only to patients, who are spared ineffective and toxic therapies, but also to the healthcare system, potentially reducing significant costs.

While healthcare costs in the United States continue to increase, the overall cost of cancer care is rising at twice the rate of healthcare costs. The cost of new drugs is the most significant factor, along with current hospital incentives that influence prescribing practices. Precision medicine relies upon individual patient genetic profiling, biomarker identification and validation, and big data research that require significant investments. Latest discoveries driving the precision medicine approach outpace the current healthcare industry’s ability to implement new findings in the clinic. Furthermore, before precision medicine is universally applied in healthcare practice, lingering practical and policy issues need to be examined and resolved. From a public policy perspective, there is a demand to adopt precision medicine technologies across the healthcare spectrum as long as clinically useful data exists. However, the extent to which discoveries from genomics research are integrated into the clinical setting, and translated into the improved health of patients,
is greatly influenced by policy decisions guiding both clinical research and healthcare reimbursement.

The Innovation Center for Biomedical Informatics (ICBI), Otto J. Ruesch Center for the Cure of Gastrointestinal Cancers, and Health Policy Institute (HPI) at Georgetown University convened a workshop to investigate the barriers to implementing precision medicine for cancer in the clinic, with an emphasis on use of big data to provide evidence for appropriate use of targeted therapies and public policy. The workshop explored these barriers from three perspectives: (1) clinical utility, (2) reimbursement, and (3) the health economics of precision medicine versus standard of care.

These perspectives inform our knowledge of barriers to provider/clinician use and payer reimbursement of molecular testing for personalized medicine in cancer. The invited stakeholders were an interdisciplinary group of experts including oncologists using molecular profiling for their patients, lab developed test (LDT) providers from academia and industry, health economist as well as an interview with a clinician representative from a payer. The goals of the workshop were:

1) to explore the role of big data to accelerate innovation and use of precision medicine in the clinic,
2) to identify primary barriers to precision medicine adoption in the clinic and
3) to determine the actions stakeholder communities should take in order to advance precision medicine.

Role of Big data to accelerate innovation in precision medicine
Currently available therapeutic choices in many hospitals and clinical institutions are limited to assays and drugs that have been approved by the U.S. Food and Drug Administration (FDA) or currently part of a clinical trial. Yet, precision medicine promises to offer clinicians and their patients the latest developments in medical care. Big data is at the heart of informing precision medicine. Paradoxically, the precise treatment plans made possible through high throughput testing (such as Next Generation Sequencing, NGS) are also stymied by the volume of disorganized and fragmented data buried in the biomedical literature and conference proceedings, including Electronic Health Records (EHRs) and clinical trial databases. Ongoing efforts such as ClinVar and ClinGen to identify and link clinically relevant phenotypes to genetic variations promise to standardize the massive amounts of genetic data and make it available to the clinical and research communities to improve patient care.
The workshop participants identified seven key barriers to the widespread adoption of precision medicine as shown in Figure 1.

A breakout discussion focused on defining the top two barriers, articulating the overarching causes of each barrier, describing the impact the barrier creates, and proposing solutions to address the barrier (Tables 1 & 2).

**Actions required by stakeholder communities in order to advance precision medicine.**

We defined potential solutions to enable the research and healthcare communities to address research gaps and overcome specific barriers. Our discussions are summarized below under the three broad perspectives

(i) clinical utility,

(ii) reimbursement, and

(iii) the health economics of precision medicine versus standard of care.

**Clinical Utility**

Clinical utility defined as the usefulness of a test to provide information about diagnosis, treatment, management, outcomes, or prevention of a disease — is an important hurdle facing technology developers and investors of molecular testing today. Therefore, payer systems are most interested in the clinical utility of new molecular/biomarker assays. For such assays that have not been approved by the FDA, the clinical research team must determine the appropriateness of a potential biomarker. In the absence of a long and costly clinical trial, these decisions have to be made primarily based on reviews of peer-reviewed literature and conference proceedings. However, most molecular assays today are introduced to the marketplace with incomplete knowledge (i.e. lack of data) about their impact on healthcare costs or their ability to improve health outcomes compared to standard care. There are currently no universally accepted recommendations for validating the different types of biomarkers. This makes it difficult for physicians deciding how to apply new findings in their patient care — the crux of the clinical utility dilemma. Moreover, health insurance plans consider medical necessity in making coverage and benefit decisions. In molecular diagnostics it is challenging to determine medical necessity because the clinical evidence associated with the assays for known actionable targets is fast emerging and in most cases inconclusive.

For example, a physician cannot really prove a Computerized Tomography (CT) scan is medically necessary each time one is done, but it has become conventional in practice. Therefore ‘medical necessity’ justification is rarely required. Molecular profiling is headed in the same direction. The Chem 20 blood test given to patients during a physical is another good example; this test comes in a bundle and all markers have been studied, but one cannot really prove all 20 of those chemistry tests are needed for each patient. The cost of doing 15 versus 20 chemistry panels is negligible and the additional available tests may provide valuable information. The same can be said for multi-omics profiling. There are no cost.

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<thead>
<tr>
<th>Table 1. Barrier 1 – Lack of data showing clinical utility</th>
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<tr>
<td><strong>Barrier Causes</strong></td>
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<td>- Technical limitations and lack of sufficient quality control across laboratories (e.g., testing and analytical heterogeneity, wet/dry laboratory limitations)</td>
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<td>- Lack of NIH funding for precision medicine</td>
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<td>- No stand-alone business model exists for demonstrating value without also having a companion therapy in development</td>
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<td>- Payers averse to risks in changes and variability in health care costs</td>
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<td>- Difficulty in establishing post-analytic value without a clinical trial</td>
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<td><strong>Barrier Impacts</strong></td>
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<td>- Lack of use, or inappropriate use, of molecular testing for precision medicine</td>
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<td>- Emerging evidence of benefit is not fully utilized or planned for use by the payer</td>
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<td>- Payers do not want to reimburse precision medicine without evidence of value (both in terms of health outcomes and costs)</td>
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<td><strong>Potential Solutions</strong></td>
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<td>- Identify possible funding models for precision medicine that do not rely on the pharmaceutical industry. Model would need to engage payers, and focus on developing evidence ultimately impacting payer costs. Federal funding is always desired, but in the current economic climate, may not be tenable. The funding model would need to be constructed in a way to avoid conflicts of interest.</td>
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<td>- Design innovative trials and develop evidence acquisition methods that will help shape the levels and types of evidence available for regulatory consideration.</td>
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<td>- Develop and operationalize data sharing model that links de-identified open or closed access data to reimbursements. Variables to consider: HIPAA compliance; patient consents; Genetic Information Non-Discrimination Act (GINA) implications; possible model: NCI/NCBI data repository (ClinVar star system for variant level data curation); tiered levels of access to summary and record level data.</td>
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savings in testing small subsets of genes in comparison to a panel of actionable and experimental biomarkers. In fact, it may cost more to sequentially test for small subsets of genes and the tissue may be exhausted. Including multi-gene panels in routine testing may uncover prognostic patterns from patient’s tumors that can be used to help counsel patients and understand cost to help with yes/no decisions on treatments. Professional societies and national organizations involved in precision medicine will need to take the lead in technology assessments to provide guidance to stakeholders applying and paying for these tests. Only then will the field of precision medicine move to a point where we can test multi-gene and even multi-omic panels to improve precision in healthcare decision-making.

Reimbursement by Private Insurers

The current healthcare reimbursements of precision medicine are typically cost-based instead of value-based. The costs of molecular profiling are much higher than traditional laboratory tests (e.g. metabolic tests). However, the value of information generated can be significant if clinical decisions affect health outcomes and financial cost. Payers often treat the costs of both types of tests similarly, so reimbursements for molecular profiling can be paltry compared to the actual cost, and more importantly, value. A lack of standardized metrics, including cost effectiveness and health technology assessments, has made it difficult for manufacturers and laboratories to recoup development and validation costs and limits incentives to develop such tests. The transformation in healthcare towards paying providers based on outcomes rather than on volume of services provided is moving more payers towards bundled reimbursements. One model that might enable accurate reimbursements for cancer care is being implemented by COTA (Cancer Outcomes Tracking and Analysis), Inc., through digital mapping of all cancers within its CNA (COTA Nodal Address) system – a standard for precisely classifying cancer patients. For examples, patients are assigned a CNA based on the disease type, stage, grade, hormonal status (in the case of breast cancers) etc. More than 2,000 COTA nodal addresses have been grouped into 6 bundles, used for precertification. The result is an objective standard to aid in proper diagnosis and precision treatment, assessment of risk, and improvement of clinical outcomes and cost. CNAs, which supplement ICD-10 (International Statistical Classification of Diseases and Related Health Problems) as the basis for reimbursement, are part of a cloud-based platform that is moving reimbursement models away from a fee-for-service to value-based reimbursement models.

A central point in the discussion about the lack of data was that there is no current incentive for payers to contribute to precision medicine development. There is a sense of urgency among payers and test developers to get enough information to show that broad testing (multi-gene) rather than a la carte testing of individual analytes will prove useful. Broad testing may help pay for a clinical trial, and uncover new information about treatment options. If done early enough, the cost-benefit of precision medicine is in the payers’ favor because the tests can help avoid costly trial and error based treatments and may help avoid complications. These incentives must be evident to engage payers and motivate insurance companies to contribute to research. Molecular tests should be administered first, rather than after all conventional options have failed.
Health economics perspective

Precision medicine creates value through two channels. First, it helps identify “non-responders”. Some non-responders would have obtained treatment with trial and error. By identifying non-responders prior to treatment initiation, precision medicine avoids unnecessary care and associated health care costs. Second, it helps identify “responders”; some responders would not have obtained treatment with trial and error. By identifying responders prior to treatment initiation, precision medicine converts treatment from a gamble (that might give you toxic side effects or improvement in health) to a certainty with guaranteed improvement in health. This reduction in uncertainty encourages responders to seek treatment, consequently improving their health. Thus, precision medicine has the potential to significantly improve cancer treatment – a game changer, not only for cost savings but improved health outcomes. Molecular diagnostics companies have been pressing the cost-benefit issue with payers, asking why companies would pay tens to hundreds of thousands of dollars to cover cancer therapies using the standard trial and error approach, but hesitate or deny coverage for a $3,000-10,000 test that may more strategically identify therapies likely to be successful for an individual patient. Many private insurers use the Center for Medicare and Medicaid Services (CMS) payment schedules as a benchmark for reimbursement of molecular testing. This payment schedule is cost based and does not recognize the value generated by molecular testing.

While the clinician focuses on health and medical interventions to maintain or restore health, economists use models to measure the combined value of health – quality of life, contribution to society (productivity and purchasing power), and the total costs associated with care. As noted above, precision medicine generates value by changing treatment decisions, possibly impacting quality of life. However, value is dependent upon perspectives - as such, payers are not yet incentivized to promote precision medicine tests that increase healthcare costs in the short term, despite the fact that health status and quality of life may also increase, and costs may be lower in the long term. Adapting a health economic model may help justify widespread adoption of precision medicine, as it helps highlight the value generated for payers, patients and the health care system. The workshop participants suggested the possibilities of a third-party broker model, such as a data company to perform real-time health economics projections, to shift incentives, as a possible solution to this barrier.

Conclusions

In summary, despite the potential of precision medicine to transform healthcare, the adoption of precision medicine in practice has been slow, in large part due to the lack of evidence of clinical utility provided by tests. Other interrelated factors include evidence of cost effectiveness, limited insurance coverage, and lack of an appropriate regulatory framework. The issues addressed in this study paper include concepts for understanding if precision medicine will raise or lower the cost of healthcare; the current policy framework for molecular test coverage by private payer plans; and the incentives or disincentives that exist for adoption by insurers and providers. Empirical evidence is scant, in large part because only few studies include a cost-benefit analysis comparing precision medicine to standard of care. There are numerous small-scale studies that show precision medicine will significantly lower costs, improve medication adherence, and enhance quality of life.

Precision medicine research is something the payers should consider supporting. One possible approach for payers to support research would be to contribute data for rigorous research on comparative effectiveness, outcomes and medical necessity. They should also be more consistent and accurate in reimbursement for cost of molecular tests and treatments identified by tests. As patient clinical diagnostic data accumulates at health centers, this provides a unique research opportunity into outcomes and benefits of targeted therapies. Also, such research presents a huge opportunity to determine how molecular testing is influencing patient-physician decision making with regard to treatment plans. There is the potential for huge payoff from a health economics standpoint. As insurers look for cost cutting strategies, this approach may make sense. For example, if a physician orders a $3,000 test for a patient to determine if a $100,000 drug will be effective, that could lead to significant cost savings for the payer, while ensuring patients are not unnecessarily exposed to drugs – and their side effects – that may not lead to positive outcomes. From a health economics perspective, it may lead to higher return on investment if payers invest in the science. There are some caveats to retrospective analysis of aggregated patient molecular testing data by payers. Such analysis may not fully account for bias, performance status, and timing of the testing relative to other therapies. So the conclusions drawn from these sorts of data aggregation studies would need to be validated through observational studies using electronic medical records and/or prospective, randomized controlled trials. Possible funding models for precision medicine should not rely solely on biopharmaceutical industry sponsors. Payers should be engaged with a focus on developing evidence ultimately impacting payer costs. Federal funding is always desired, but in the current economic climate, this may not be tenable. The funding model would need to be constructed in a way to avoid conflicts of interest.
Role of professional societies

Professional societies, representing various scientific communities at large, will play a critical role in shaping precision medicine by providing policy positions, and informing and educating their membership on the latest research developments. The Association for Molecular Pathology (AMP) is at the forefront of policy discussions – and has been for many years before precision medicine hit the national spotlight – through numerous engagements with the FDA on issues surrounding the regulation of molecular testing. The American Society of Clinical Oncologists (ASCO) and American Association for Cancer Research (AACR) are the leading educational authorities for cancer researchers and clinicians worldwide that work with AMP and other organizations to develop guidance on the use of molecular testing for various cancers. The National Comprehensive Cancer Network (NCCN) also develops cancer treatment guidelines, and gives clinicians access to tools and knowledge that can help guide decision-making. Established in 1999, the International Society of Personalized Medicine (also called the Personalized Medicine Coalition, PMC) has very actively promoted precision medicine through education and advocacy with a number of informative white papers. These societies and many others all play a vital role in moving the frontiers of science forward through education and importantly, advocating policy decisions that encourage research progress and timely access to the fruits of early discovery. Considering the pace of research, these societies face a challenge in presenting simplified and unified guidance to physicians on available molecular/biomarker assays, the clinical utility of these assays, and communicating their value to payers. The important conversations have started and there is evidence that stakeholders from all parts of the equation are already beginning to work together to realize the exciting potential of precision medicine.

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