New Genomic Technologies in Clinical Medicine: Current Evidence and Decision-Making

Summary and Highlights from the Green Park Collaborative Genomic Technologies Forum, November 2 and 3, 2017
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ABOUT CMTP
The Center for Medical Technology Policy (CMTP) is an independent, non-profit dedicated to developing a health care system where patients, clinicians, health care policymakers, and payers have the evidence they need to make informed health decisions. We convene and collaborate with a national and international network of thought leaders, patients, patient advocates, clinicians, policymakers, and payers. Together, we support the next generation of clinical research. We do this by providing methodological guidance, shaping health policy solutions, and transforming clinical research.

ABOUT GREEN PARK COLLABORATIVE
CMTP launched the Green Park Collaborative (GPC) in 2013 as a neutral forum to guide the creation of the clinical evidence needed to inform healthcare treatment and coverage decisions. Participants include a diverse mix of payers, life sciences companies, patients, clinicians, researchers, regulators, and other stakeholders. GPC convenes working groups to develop study design recommendations that focus on real-world effectiveness and value, meet the evidence expectations of payers, and are informed by the views of patients and clinicians.
PREFACE

In 2013, the Green Park Collaborative (GPC) released recommendations for demonstration of clinical utility of molecular diagnostic tests in adult oncology. Initially funded by the WellPoint Foundation (now Anthem), and completed with contributions from a pre-competitive consortium of life sciences companies, the effort took roughly two years and involved dozens of stakeholders and experts providing input into the work products of a core technical working group. These recommendations provided guidance on methods that would produce the evidence of clinical utility needed by many payers and decision-makers in what we refer to as the “post-regulatory” space; i.e., payers, patients, and providers, and others who need to make decisions in the aftermath of applicable regulatory processes (if any). This was a signal accomplishment in achieving near-consensus on a range of evaluation methods for clinical utility that include but also move beyond randomized controlled trials. Even so, the rapid development and evolution of high-throughput sequencing techniques such as next generation sequencing (NGS) made the recommendations seem too focused on traditional molecular diagnostics almost as soon as they were published.

Encouraged by numerous stakeholders, GPC then tackled questions around clinical utility for next generation sequencing (NGS) and other high-throughput sequencing techniques, particularly in the context of cancer care. What makes these techniques different from traditional genetic testing, and what are the challenges for demonstrating clinical utility? In so doing, we found that certain questions of policy consistently hindered discussion of appropriate evidence in this context. For example, it was difficult to discuss how to demonstrate clinical utility of NGS-based gene cancer panels if there was disagreement on whether a panel having only a subset of genes relevant for a given indication could ever be considered to have utility for that indication. Hence, GPC ultimately produced a set of Medical Policy and Model Coverage Guidelines for Clinical NGS in Oncology in 2015, which suggested that the door could be opened to coverage of NGS-based panels under carefully defined circumstances. It also recognized that the recommendations offered in the report could be realized more rapidly with enhanced high-quality data-gathering for more rapid progress in genomics research and better transparency in laboratory testing methods and standards, among other issues.

Since the release of the Medical Policy and Model Coverage Guidelines, the GPC has worked to promote the conditions needed for wider implementation of the policies recommended. This Genomics Technology Forum represents a key part of these efforts. By fostering multi-stakeholder dialog around emerging technologies, by hearing about developments in healthcare spaces where innovation is happening, and by engaging with front-line clinicians on what they need to implement genomic advances, we create a “state of the field” view for stakeholders to identify challenges and embrace opportunities earlier in product development. This meeting was intended to provide an early learning opportunity for all stakeholders in the genomics ecosystem grappling with the need to balance the promise of these innovations with cost, clinical utility, and practice considerations.

Emerging sampling and analytical technologies hold great promise for advancing human health. Yet in the race to bring promising innovation to patients and develop more effective ways to treat and prevent disease, evidence development to support clinical decision-making often lags. This meeting gathered more than 65 stakeholders representing private and public payers, government, industry, researchers, clinicians, and patients, asking a variety of questions including:

- What clinical applications are emerging for omics-related technologies? What evidence exists to support these uses?
- What decisions are health plans making for these technologies and why?
- What omics-related innovations are health systems introducing into care and what kinds of evidence are they collecting?
- How can we close the gap between innovation and evidence for decision-making?

What follows is an account of key information presented by our speakers, panelists, and discussants. In some ways, our discussions raised as many questions as they answered. But a continuing dialog between stakeholders is essential to promote better understanding of new innovations and how to make them appropriately accessible for the benefit of patients as quickly as possible.

Several CMTP staff members were instrumental in the planning and execution of the Genomics Forum. Sincere thanks go to Program Manager Jennifer Al Naber, Senior Research Manager Robert Conley, Marketing and Event Manager Julie Simmons, and Executive Assistant Janelle King. John Beilenson of Strategic Communications and Planning (SCP) developed key sections of the summary and related communications materials. We would also like to thank the extremely helpful staff at the Kimpton Hotel Monaco Baltimore and the audiovisual team from Production Resource Group.

In addition, we gratefully acknowledge the support of generous sponsors who made the event possible (full list provided below). We look forward to continued collaboration with these and all the critical stakeholders gathering to discuss new challenges in evidence and clinical medicine through the Green Park Collaborative.

Donna A. Messner, Ph.D.
Senior Vice President, Center for Medical Technology Policy
Program Director, Green Park Collaborative
SPONSORS
GENOMICS AND LIQUID BIOPSY: CONCEPTS AND CLINICAL PERSPECTIVES

SPEAKER
Matthias Holdhoff, MD, PhD
Assistant Professor, Brain Cancer Program, Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine

The first afternoon of the meeting focused on liquid biopsies, a fast-developing technology that analyzes blood for cells and DNA fragments shed from tumors. Dr. Holdhoff introduced the topic and provided a scientific overview for the multi-stakeholder audience, reviewing the rising interest in targeted therapies (starting especially with the remarkable success of Gleevec in chronic myelogenous myeloma), the first full sequencing of the human genome, and the explosion of new data and innovation that have followed as sequencing has become radically faster and cheaper. With these developments, and advances in the study of tumor biology, thousands of potentially significant gene mutations connected to cancer have been identified. However, studying each of these targets is daunting; out of the many thousands of potential targets identified, relatively few have become clinically usable targets for drug therapies.

Liquid biopsy, he said, has the advantages of being non-invasive, allowing multiple specimens to be taken easily over time, obtaining a fresh source of DNA. It does not suffer from the type of sample bias associated with tissue biopsy (where for highly heterogeneous solid tumors the result can depend on where the tumor happened to be sampled). It also creates the promise of using extremely sensitive assays to detect and monitor cancer. Individual circulating tumor cells shed by solid tumors can be collected, counted, and analyzed for DNA, RNA, and proteins. They can also be cultured for research and drug development. Advances in digital genomics allow DNA fragments released by damaged or dying tumor cells (cell-free DNA) to be collected and distinguished from normal DNA in the blood by individually sequencing each fragment found in a sample. He reviewed the methods used for this sequencing and examined the overall advantages and disadvantages of each class of methods.

Potential applications for liquid biopsy, Dr. Holdhoff noted, include:

- Determination of mutational status, molecular heterogeneity of the disease overall
- Monitoring of disease burden / tumor dynamics
- Evaluation of early treatment response
- Tracking resistance in real time
- Detection of minimally residual disease
- Early detection

However, to underscore the work needed to be done to develop liquid biopsy for clinical use, he surveyed evidence for a proof-of-principle for the use of cell-free DNA with cancer biomarkers in three different disease areas: breast cancer, colorectal cancer, and gliomas. These examples illustrated that the detectability of cell-free DNA can vary by tumor stage, grade, and location. In some cancers (such as in the colon) it may be usable as a measure of disease burden, a detector of tumor resistance, and an indicator of the need for adjuvant therapy following surgery. For other cancers (e.g., gliomas) it is only rarely detectable in blood and only for the most invasive tumors, limiting its use.

While good proof-of-principle data exists in each of these cases, what is needed, he said, is more prospective validation, that is, large scale studies to determine the value of circulating tumor DNA and
circulating tumor cells, gathered through liquid biopsy, for clinical practice. To get there he suggested the field:

- Dedicate funding and personal resources for large-scale companion studies in conjunction with prospective clinical trials;
- Standardize specimen sampling, processing and storage;
- Start with straightforward, simple question studies to optimize methodology; and
- Involve liquid biopsy experts early in clinical trial design.

PANEL DISCUSSION 1: EVIDENTIARY STANDARDS FOR LIQUID BIOPSY TECHNOLOGIES
The first panel looked more deeply into the types of evidence needed to support clinical use of liquid biopsy from the perspective of the FDA, payers, and others.

SPEAKERS

Jim Almas, MD
Medical Officer, Coverage and Analysis Group
Centers for Medicare and Medicaid Services

Rick Lanman, MD
Chief Medical Officer
Guardant Health

Robert McDonough, MD
Senior Director for Clinical Policy Research and Development, Aetna

Bruce Quinn, MD
Principal
Bruce Quinn Associates LLC

Reena Philip, PhD, Director
Division of Molecular Genetics and Pathology
Food and Drug Administration

Girish Putcha, MD, PhD
Director of Laboratory Science
MolDX, Palmetto GBA

Hannah Mamuszka, Moderator
Founder and CEO
Alva10

TWO CASE STUDIES TO REVIEW
The group examined two contrasting cases representing differing approaches to evidence development to support liquid biopsy.

The first case study was the cobas® EGFR v2, which is used for testing circulating tumor DNA in non-small cell lung cancer (NSCLC). This was the first liquid biopsy-based diagnostic approved by the FDA. In a pivotal clinical trial, patients were enrolled based on an already-validated tissue biopsy test for EGFR and then retested with the liquid biopsy diagnostic. Through this “bridging” study, not only was the concordance between the two diagnostic techniques determined, but progression-free survival benefit from marker-based treatment of patients was also measured. This study concluded that there was substantial benefit to erlotinib therapy in patients who test EGFR-positive by the cobas® test. In the clinical trial, the sensitivity of the test (the true positive rate) was only 76.7% while the specificity (true negative rate) was 98.2%. Since the test is better at detecting those without the mutation than those with it, the FDA approved this as an initial screening test: patients with metastatic NSCLC who test positive for an EGFR mutation by the cobas® test should be treated with erlotinib; those who test negative should be tested by tissue biopsy for confirmation of mutation status.
The second case focused on the use of a liquid biopsy test to identify HER2 mutations in circulating tumor cells (CTCs) as an alternative to traditional tumor tissue cultures in breast cancer. Several anti-HER2 therapies have shown great promise, but a sizeable subset of HER2-positive patients do not respond to these drugs. The study used a convenience sample of patients already determined to be HER2-positive and planning to receive anti-HER2 therapy plus chemotherapy. It found that the presence of CTCs in HER2-positive patients identified through liquid biopsy was positively correlated with better response to anti-HER2 therapies and significantly improved progression-free survival. As noted above, this study only conducted CTC testing on patients already selected for therapy by tissue-based HER2 testing. Although a correlation was found between the presence of CTCs and improved response to therapy, no direct comparison was made between the ability of CTCs vs. tissue-based HER2 testing to guide selection of patients who would benefit from treatment. The question for the group was whether this level of evidence was appropriate for clinical decision-making and under what circumstances.

STAKEHOLDER PERSPECTIVES

The group heard brief presentations offering perspectives on the cases from representatives of public and private payer organizations, FDA, a liquid biopsy testing company, and an expert health business strategy consultant. Discussion points from these presentations, and the wide-ranging conversation that followed, included:

About Evidence Requirements

For Case 1, most participants said the FDA’s decision to put liquid biopsy testing first and confirm negative results with tissue biopsy was sensible. Dr. Quinn called it the “easiest solution” but added that it may not always be practicable. Dr. Almas noted that while Medicare coverage for the test is at the discretion of regional contractors (i.e., is not undergoing a National Coverage Determination), the supporting studies are of the type Medicare likes to see. Dr. Putcha asked whether this type of test should be considered as valuable as tests that can serve to rule-in and also rule-out candidates for treatment. He also suggested that studies of diagnostic tests that rely on duration-related outcomes like progression-free survival or overall survival tend to obscure the validity of the test because the efficacy of the drug is “baked in” to the outcome. For utility, however, others expressed a wish to see survival-related outcomes.

Case 2 was generally seen as having weaker evidence. Dr. Putcha noted that the evidence supports a prognostic claim, but the intended use is predictive. Dr. Phillip likewise noted in her slides that a “difference in prognosis does not establish that patients should be treated differently.” Both also said the intended use of the test should guide the way the studies are designed. As Dr. Putcha noted, “What is actually being measured, why, and on whom?” Dr. McDonough added that this was more of a “hypothesis-generating” study; for the predictive claim, there would need to be prospective clinical evaluation, not just a correlation study. Others noted that while the prognostic value generated by liquid biopsies (and other assays) is not the same as predictive value, prognostic information may have great value to patients. Even so, the evidence had other faults. Drs. Almas and Phillip both expressed the need for analytical studies to support specific cutoff points (how many cells need to be found to make a prognosis?). It was also noted that little clinical outcome information is available on patients who test negative by tissue and positive by liquid biopsy because many studies include only patients who test positive by tissue. This is a potentially important gap in the way studies are often done.
When might it be possible to avoid doing difficult and expensive prospective outcomes studies of the type done for Case 1? Dr. Lanman suggested, and some others agreed, that prospective outcome studies should not be necessary in cases where the efficacy of a drug-variant combination has already been established for tissue biopsies. In these cases, demonstration that the variant can be reliably detected in liquid biopsy should be sufficient to establish its predictive value. If there is no tissue comparator, then more rigorous outcome studies are needed.

About Payment
Additional discussion points related to payment for liquid biopsy testing included the following:
- CMS national coverage decisions (NCS) look at a variety of predictable factors, but are not often done. Eighty-five percent of coverage decisions take place as individual judgements of regional Medicare contractors on the local level. Seeking an NCS may create significant risks for test developers if the application is denied, since the decision will automatically apply across all the local regions.
- There is inherent utility in avoiding a repeat invasive tissue biopsy. That said, how many repeat liquid biopsies will an insurer cover over a lifetime? Standard practice calls for rebiopsy at disease progression, but decisions to cover monitoring a patient every two months to gauge response to therapy or to identify early development of resistance mutations will require more rigorous evidence of utility.
- Payments in most of our fee-for-service health system are siloed. Liquid biopsies and other tests are paid for from one bucket, drugs from another, acute/clinical care from another. While the move to value and population health may help, there are not incentives currently to assess the true global value of diagnostics, which would include tests, drugs, and care together.

MOLECULAR MARKERS AND GENOMICS IN COMMUNITY ONCOLOGY

SPEAKER
Satish Shah, MD
Medical Director and Founder
Gettysburg Oncology Center

Dr. Shah provided a perspective grounded in his day-to-day practice over 30 years caring for patients with a variety of cancers in central Pennsylvania. His presentation started with a review of the various diseases he treats, the relevant genetic testing they typically do, and the major laboratories they have used for tumor genotyping. It is an exciting time in cancer care, he noted, as there are many treatments available for different cancers, but significant challenges remain.

Dr. Shah presented three case examples to illustrate how tumor profile reports can sometimes be useful but also confusing to practicing clinicians. In one example, the same targeted therapy was identified as both of “likely benefit” and of “unlikely benefit” in the same patient’s test report. This was based on two different biomarkers having contradictory interpretations. In another example, a standard therapy known to be widely effective in the underlying cancer as a 1st-line agent was listed as of “unlikely benefit.”

For Dr. Shah, the test reports tend either to confirm the guideline-directed care he already intended to deliver (e.g., 5-FU and leucovorin in a colon cancer patient) or to suggest an alternative pathway (or sometimes alternative diagnosis) for a patient in whom conventional treatment options are not working. He said guidance should be available to help clinicians better use the data. However, for initial
treatment in newly diagnosed patients, Dr. Shah often finds the tests wanting. Oncologists want the first drug administered to a newly diagnosed patient to deliver the maximum benefit possible. Among the several guideline-directed therapies available for a given patient, which of those therapies would be most effective to give first? This is the information Dr. Shah would like to have. This perspective exposes a significant gap between the information desired and that which can be supplied based on current knowledge.

In addition, he noted, while test reports often provide listings of clinical trials related to identified biomarkers, it is often not simple to specifically identify trials in the region for which the patient in question would qualify. He made an appeal for laboratories to provide clearer, straightforward information more directly tailored to the patient’s condition and location.

More generally, Dr. Shah noted that tumor profiling can be made more relevant in a clinical setting if there were:

- Better and clearer data reporting, which is critical for both treatment decisions and communication with patients;
- Available cost information and patient-reported outcomes that can help guide decision-making around different treatment options; and
- More rapid rolling up of new knowledge into clinical guidelines, which facilitates payment for treatment and will help drive broader practice change.

In the Q and A that followed Dr. Shah’s presentation, the role of patient advocacy organizations was also raised. These groups can provide important impetus to promote the information priorities of cancer patients (as opposed to payers or industry) and drive research towards the questions derived from the personal experience of care.

**GENOMICS AT NCI: WHAT’S IN STORE**

**SPEAKER**
Jean Claude Zenklusen, PhD
Director, The Cancer Genome Atlas
National Cancer Institute

While Dr. Zenklusen’s presentation focused on the cutting-edge 21st Century technologies that are making The Cancer Genome Atlas (TCGA) possible, he began by noting that personalized medicine is not a new idea. He said it is 3,000 years old, as old as Hippocrates, who believed that the person was more important than disease. Today, however, with genomics and related technologies, he offered, we have the information to make personalized medicine a reality.

First piloted in 2005, TCGA is an increasingly important tool in this effort. It is a collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) that has generated comprehensive, multi-dimensional maps of the key genomic changes in 33 types of cancer. The TCGA dataset, comprising more than two petabytes of genomic data, has been made publically available, and this genomic information helps the cancer research community to improve prevention, diagnosis, and treatment efforts.
Connected to the TCGA dataset is the Cancer Data Commons (CDC), which provides researchers with a unified data repository that enables data sharing across cancer genomics studies in support of precision medicine. Open source, the CDC allows researchers to validate and submit biospecimen, clinical, and molecular data and metadata and compare it broadly to relevant datasets. In 2017, CDC will add data visualizations to its already impressive reporting capabilities.

While there will not be a TCGA 2.0, Dr. Zenklusen said several new programs are already underway, including the Exceptional Responders Initiative, ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial), Cancer Driver Discovery Program, and the Clinical Trial Sequencing Program. The focus of these projects is discovering the reasons why some patients respond better than others to therapy and to learn more about the molecular underpinnings in the process. “The big message,” said Dr. Zenklusen, “is cancer genomics is here to stay, but in the context of helping decipher how to better treat the patient.”

PANEL DISCUSSION 2: GENOMICS CLINICAL TRANSLATION: INNOVATIVE HEALTH SYSTEMS

SPEAKERS

Sunil Budhrani, MD, MPH, MBA  
Chief Medical Officer and Chief Medical Informatics Officer  
Innovation Health

Debra Leonard, MD, PhD  
Professor and Chair of Pathology  
University of Vermont College of Medicine

Marc S. Williams, MD, FAAP, FACMG, FACMI  
Director of the Genomic Medicine Institute  
Geisinger Health System

Christine Lu, PhD, Moderator  
Professor, Department of Population Medicine  
Harvard Medical School and Harvard Pilgrim Health Care Institute

Health care reform has led to integration of patient care and coverage and other structural changes in large pockets of the health care system. Hospitals and medical practices in more traditional arrangements must adhere to the relatively limited coverage policies of traditional health plans with respect to genomic testing. These policies protect patients by requiring high-quality evidence of effectiveness. But it can take years for the required studies to be developed, published, reviewed by guideline committees, and finally adopted by health plans. By contrast, these new health system structures can create incentives and flexibility to innovate in care delivery. By collecting their own data to demonstrate effectiveness, gains in patient benefit, and cost effectiveness of care, more rapid learning can take place. Integrated health systems can therefore serve as incubators of both clinical innovation and evidence development in a way that traditional systems have not been.

Convinced that genomics will become an integral part of care decision-making in the future, some health systems are making substantive investments in systematic collection of genomic information and incorporation into certain clinical programs. For this panel, representatives of three such health systems described their programs, what it takes to implement them, and what they are learning so far.

INNOVATION HEALTH: BUILDING A ROBUST GENOMICS CAPACITY

Innovation Health, a new partnership between INOVA, a provider, and Aetna, an insurer, serves more than two million patients each year in northern Virginia, with plans to expand in the mid-Atlantic region. Dr. Budhrani said this joint venture combines the care delivery of Inova with the actuarial expertise of
Aetna. With a developing concern for population health, it has set out to be “a global leader in the science of genomics and the new era of personalized health.” As such, it has made significant investments in a broad-based genomics capability.

An early opportunity for developing this capability was in the area of pharmacogenetics. Innovation Health is offering free pharmacogenetic testing on 7 genes related to sensitivities for 21 medications for all infants born in their hospitals. With this genetic information in the patients’ records, clinical outcomes will be followed over time to gain a better understanding of the genetics of patient response to these drugs. The aim is for drug response increasingly to be predictable, allowing for better tailoring of the right drug at the right dose for individual patients. Other opportunities for pharmacogenetics include behavioral health, and cancer, where individual drug response to chemotherapy can reduce adverse events and related readmissions, reducing readmission penalties in bundled payments schemes.

Innovation Health also offers cancer patients genetic tumor profiling on a panel of 50 cancer-related genes. Such targeted testing is increasingly available on a widespread basis, but Innovation Health sees cancer care also in public health terms: better understanding of heritability and cancer risk can lead to prevention strategies.

UNIVERSITY OF VERMONT HEALTH NETWORK: GENOMICS IN AN ACADEMIC HEALTH SYSTEM

The University of Vermont Health Network encompasses six hospitals and two Accountable Care Organizations, as well as the University of Vermont Medical Group, and is affiliated with the University of Vermont College of Medicine. This unique configuration was facilitated by the 2011 Green Mountain Care Law, a forward-thinking bill passed to integrate and improve care and lower costs in the region (and statewide).

One vision of the network is “genomes for all” by 2023, said Dr. Leonard, a professor at the University of Vermont College of Medicine, because the genome represents fundamental health information that should be included in patient records for learning over time. Accordingly, the Network is developing a substantial infrastructure for laboratory, bioinformatics, and educational services. Like Innovation Health, UVHN sees genomics as a strategy towards improving cost-effective care, with an initial focus on areas where some progress has already been made. In oncology, cancer gene panels of 25-50 genes are offered for solid tumors, hematologic malignancies, and inherited cancer. The tests will be integrated into clinical care pathways with multidisciplinary clinical teams assessing and acting on results. In pharmacogenomics, panels of 50 to 80 genes are available. They will soon move on to heritable disorders where, she anticipates, whole genomes will eventually be run (not solely exomes, since the cost difference is likely to be small and non-coding regions of the genome are now known to cause disease). There are a range of genomic studies and educational initiatives underway, she said, as well as broader community education to build patient/consumer support for this effort. As Dr. Leonard noted, “The genome is a journey, not just a test.”

GEISINGER HEALTH SYSTEM: GOING GENOME FIRST

At Geisinger Health System (GHS) in Pennsylvania, Genome FIRST™ is part of a multi-faceted initiative in which 250,000 Geisinger patients will ultimately have their exomes sequenced. Framed as a community health initiative, participants sign broad consent to combine de-identified information from their patient file with biospecimens in a biorepository. They also agree to be re-contacted for future projects and communication of results. The effort will look for medically actionable results in those data and then return results to patients and providers. In turn, Geisinger will follow up and provide support and long term care management planning.
Genome FIRST™ was first launched in 2007, with exome sequencing of about 53,000 patients to date. To start, the program is looking at variants of 76 genes associated with 27 conditions (including the 56 genes recommended for disclosure by the American College of Medical Genetics), with initial prioritization of conditions for which sufficient information is available for patient management: familial hypercholesterolemia, Lynch Syndrome, and hereditary breast and ovarian cancer. The goal is to move towards a proactive care paradigm in which the initial clinical encounter comes from the finding of a variant (rather than coming from a clinical manifestation of disease). Currently, GHS pays for exome sequencing because traditional payers will not. However, if a pathogenic variant is detected, then follow-up actions and cascade screening (screening of family members for heritable conditions) can be covered because these would be medically necessary. GHS leadership support the investment, said Dr. Williams of Geisinger, because over time the result will be a robust genomics-to-care infrastructure that will drive improvement on a range of patient-centered and system outcomes.

As Dr. Liu from Harvard Medical School reflected during the Q and A, one of the common threads in all three of these exciting initiatives is the presence of forward-thinking leadership willing to invest in change and innovation in these organizations (executive leadership in the health systems and political leadership in the State of Vermont). As one participant said, “genomics and precision medicine have to be part of a [health system’s] long-term strategic plan.”

INCORPORATING GENOMICS INTO HEALTHCARE: A GENETIC COUNSELOR’S PERSPECTIVE

SPEAKER

Elizabeth Varga, MS, LGC
Co-Director of Personalized Medicine
Nationwide Children’s Hospital

Complementing Dr. Shah’s clinical perspective as well as the broader health system work to integrate genomics, Elizabeth Varga provided an important glimpse into her role as a genetic counselor who works with non-geneticist clinicians. Her work in Nationwide Children’s Hematology/Oncology/Blood and Marrow Transplant Division includes counseling patients who may need or have obtained genetic testing, or who may have genetic or heritable conditions, and consulting with their physicians.

Ms. Varga began by noting that a significant proportion of genetic counselors’ time is taken up with preauthorization procedures and paperwork required by payers for reimbursement of genetic and genomic tests. In her department, 40% of patients require letters of medical necessity. The significant administrative work load associated with billing has been driving genetic counselors out of clinical practice, she said, adding to what is already a national shortage of clinical genetic counselors. Still, based on statistics from testing in hematology and oncology in her hospital, diagnostic yields for single-gene testing are still significantly higher than for NGS-based tests, and there are fewer variants of unknown or uncertain significance. Citing an anecdote in the May 2016 edition of Front Line Genomics Magazine by Wendy Rubenstein, Varga said that while patients, families, and even non-geneticist providers (who often lack training in genetics) have growing expectations for what genomic testing can do, the results of testing are often disappointingly uninformative.

According to Varga, there are three key questions that need to be answered: 1) How can we assist providers in deciding on the right tests? 2) How can we streamline test ordering and billing in a way that
assures payers the appropriate tests are being ordered? 3) How can we assure that testing is clinically useful and does not induce harm?

To assure clinicians are ordering the right tests, Varga said multidisciplinary, collaborative care is needed along with genetic education. In addition, she recommended test utilization management programs, which have been shown capable of reducing errors in test ordering and preauthorization procedures, and reduced testing costs. This in turn prevents order error from becoming diagnostic errors for patients. These programs can also be developed in cooperation with health plans to provide streamlined billing processes for demonstrating consistent appropriate test ordering. Finally, she suggested a range of issues that can improve the usefulness of clinical testing, including education, data collection and data-sharing, multidisciplinary care teams and collaboration, research and regulation. She added that she favored regulation because she often found herself in the position of advocating against testing wanted by non-geneticist providers who were too eager to order tests when a diagnosis was available by other means.

In closing, she shared a case example of a 20-year old patient who presented with a high-grade undifferentiated sarcoma. After two relapses, tumor profiling was done and suggested possible germline genetic involvement. A complex mystery unfolded requiring examination of the family history of cancer, germline testing of family members, navigation of uncooperative family members, family politics, and privacy issues. The case illustrated the complexity of personalized medicine scientifically, legally, and ethically, and how difficult it can be to arrive at a correct genetic interpretation for counseling patients. It also demonstrated the value to patients of having genetics professionals engaged in multidisciplinary clinical teams working collaboratively to find answers.

PANEL 3: PANOMICS: THE FUTURE OF CANCER CARE

SPEAKERS

Manoj Dadlani, MEng
Chief Executive Officer
CosmosID

Don Liss, ND
Senior Medical Director for Clinical Programs and Policy
Independence Blue Cross

Vince Miller, MD
Chief Medical Officer
Foundation Medicine

Gary Palmer, MD, JD, MBA, MPH
Chief Medical Officer, President of GPS Cancer Division
NantHealth

Steve Phurrough, MD, MBA,
Medical Officer, Hospital and Ambulatory Policy Group for Medicare
Centers for Medicare and Medicaid Services

Louis Jacques, Moderator
Chief Clinical Officer and Senior Vice President
ADVI

Emerging panomic commercial testing products are based not only on DNA sequencing (e.g., whole genome and whole exome sequencing), but on measurements of biological functions within cells and other body functions. These tests combine results from varying assays with patient-specific information to create an individualized picture of, for example, gene mutation and expression within a tumor. How should the holistic biological picture created by such assays be interpreted? What evidence is needed to establish the utility of such testing and what type of evidence currently supports their use? While most
major payers have adopted a cautious approach, some health plans have developed policies to cover innovative genomics and panomics approaches under some circumstances.

In this final session, panelists discussed specific examples of payer coverage of innovative testing such as Independence Blue Cross’s coverage of NantHealth’s GPS Cancer™ (a comprehensive whole genome DNA, RNA, and quantitative proteomic sequencing test), Cigna Healthcare’s coverage policy for whole genome sequencing, and other examples.

In his introduction to the panel, moderator Louis Jacques of ADVI noted that understanding genetics has become much more complex than it was thought to be when genes first started to be sequenced and the genome decoded. While any number of FDA-approved targeted therapies with known benefits are now available, whether or how those targets work in other conditions (conditions not indicated in the labeling) is not well understood. He pointed to the SHIVA trial, for example, which found that the use of molecularly targeted agents outside their indications does not improve progression-free survival compared with physician’s choice of treatments in heavily pretreated patients with cancer.

**NANTHEALTH: PROMISE FROM THE GPC CANCER TEST**
Gary Palmer of NantHealth echoed this theme of our current limitations. We have learned how to sequence the genome, but ultimately what we want to know about is the proteins. These are the “action molecules” at work in biologic processes, said Palmer. Based on our current understanding of genetics, when we see a mutation in a gene, we infer that a corresponding mutation must be transcribed to the RNA and likewise to the expressed protein. However, until recently we have not been able to analyze proteins to a level sensitive enough to see whether these assumptions are always valid.

The new NantHealth “GPC Cancer” test not only sequences DNA and RNA, but also quantitatively measures proteins in tissue to the attomol per microgram level, which is a breakthrough improvement over existing methods. Using this technique, NantHealth has found that in some situations, mutations in DNA do not automatically translate into expressed proteins; and that, conversely, a corresponding DNA mutation cannot be found for some quantitatively expressed proteins. These uncertainties mean that in some cases of targeted testing, test results may lead to patients being treated with targeted therapies when the protein is *not* actually expressed (false positive test), or *not* being treated when the relevant protein is present (false negative). Clinical studies demonstrating these effects are yet to be done. However, Dr. Palmer noted that resistance and sensitivity proteins for chemotherapeutic agents can be detected by this method, and NantHealth has done work to characterize these proteins especially in the areas of the HER2 gene and breast cancer. This means that the GPC Cancer test can potentially turn chemotherapy —a statistical, population-based form of therapy — into a more targeted approach.

**IBC PHILADELPHIA: AN INSURER’S PERSPECTIVE**
While most major payers still consider the NantHealth test investigational, Independence Blue Cross of Philadelphia has elected to cover it under certain conditions. Don Liss of IBC described the reasons for this decision. While his group did do an evidence review, he offered primarily a policy argument. He noted that benefit plans have three major functions: establishing benefit plans; selling benefit plans to large employer groups (and increasingly individuals and government entities) and adjudicating claims on their behalf; and contracting with providers, seeking the best pricing to be able to offer affordable coverage for members.

The Affordable Care Act established essential health benefits that included laboratory services such as whole genome sequencing. For these types of services to be covered, they have to be considered
medically necessary, which means that: 1) the service is generally accepted as safe and effective by the medical community; 2) it does not cost more than an equivalent service or set of services; 3) the service is not investigational or experimental. A service is investigational if there is no evidence of effectiveness in the real world.

With these as general guidelines, health plans strive to balance the need for cost effectiveness against a felt obligation to provide members access to new innovations. Cost-wise, he said, with roughly 25 genes for which clinical utility is well-established, panels and bulk sequencing are increasingly more affordable than a series of individual tests. In addition, the drugs and biologics prescribed for treatment represent a much larger cost than testing. Hence, better tests for treatment selection will lead to better care for patients and less wasteful spending on ineffective treatments. For this reason, said Dr. Liss, his group felt existing evidence justified a “coverage with evidence development-like” policy in that systematic data collection and analysis is critically important for continued learning, and NantHealth have the data management systems in place to achieve this goal.

Dr. Liss said he felt an obligation to promote advancement of science when covering new technologies such as this one. He also noted at the beginning of this talk that roughly 50% of the oncologists working in his region are at elite NCI-designated cancer centers and another 35% are at large teaching centers – oncologists, we can assume, who are most likely to be effective early adopters of such new technologies.

FOUNDATION MEDICINE: OPPORTUNITIES IN TARGETED TUMOR PROFILING
Vince Miller of Foundation Medicine made the case that evidence is mounting for the utility of comprehensive tumor profiling in more ways than one. He said comprehensive sequencing can provide a precise estimate of the number of mutations per kilobase of DNA, i.e., tumor mutation burden, or TMB. He presented a case demonstrating that TMB is predictive of response to checkpoint inhibitors by patients with melanoma. Hence, tumor profiling may serve as a tool for predicting the patients most likely to benefit from immunotherapy, a growing and very expensive treatment option. He also pointed to an increasing number of clinical trials for targeted therapies which, he said, on the whole suggest targeted therapy is an effective strategy for cancer patients. He said that the SHIVA trial (noted earlier by the moderator as raising questions about the value of targeted therapy) was flawed because the subset of patients who had their therapy matched to DNA alterations was too small. He pointed instead to Genentech’s “My Pathway” trial, which assessed a targeted strategy for several anti-cancer agents. Of 129 patients treated, 22% with 12 different tumor types had objective responses. Recognizing the importance of recruiting patients to high quality clinical trials, Foundation Medicine has created the “Smart Trials Recruiter” to work with partner institutions to match patients to targeted trials more efficiently. Finally, he added that Priority Health, the first health plan to cover Foundation Medicine’s comprehensive genomic profiling (in October 2014) had been “excited about the opportunity to match patients to trials” – an advantage of Foundation Medicine’s approach.

THE VIEW FROM MEDICARE
Steve Phurrough explained Medicare’s approach to deciding what to pay for, underscoring that Medicare can only pay for benefits that fall into specific categories defined by Congress. The genomic and panomic tests under discussion would fall under the category of screening and diagnostic tests. For diagnostic tests, he said, laboratory tests “must be ordered by the physician who is treating the beneficiary . . . and who uses the results in the management of the beneficiary’s specific medical problem.” In addition, “ . . . no payment may be made . . . for any expenses [which] are not reasonable
and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

The judgement of whether the test is “reasonable and necessary” is typically not made at the national Medicare level, but is made by local Medicare contractors in regions around the country. Hence, if a genomic profiling test can be used by an ordering clinician for management of a specific medical problem, in theory it may be able to be covered. Palmetto has taken the lead among Medicare contractors in developing standards for coverage of sequencing-based tests. Nevertheless, coverage decision-making among these contractors may vary. Most of the Medicare-covered laboratory tests for cancer at this time do not entail panomics or large-scale sequencing; CMS believes many of these tests still lack convincing evidence of clinical utility and that treating physicians frequently do not manage patient care based on the results.

NEW FRONTIERS IN META GENOMICS
Manoj Dadlani discussed a new kind of “omics” coming to clinical practice in the future: meta-genomics, which is the genomics of a community of organisms. The human microbiome is composed of 100 trillion cells, most of which are beneficial. However, some of them are pathogenic. Infectious disease today faces many challenges, including more rapid evolution of pathogens, rising hospital-acquired infections (HAIs), and antibiotic resistance. Global deaths from antibiotic resistance are projected to rise precipitously over the next decades. His company’s technology can take different types of body samples from infected areas and conduct genomic sequencing to learn:

- Microbial Identification (sub-species & strain)
- Antibiotic Resistance
- Virulence Factors
- Relative Abundance

This can be done much more rapidly than traditional cell culturing, potentially providing information needed on infection in a matter of hours. The test is being piloted, thus far with encouraging results, and prospective studies to demonstrate clinical value are anticipated soon.

LOOKING AHEAD: NEXT STEPS IN THE CONVERSATION
In the years since GPC first began work on molecular diagnostics and sequencing, the questions have multiplied. Large commercial payers continue to register concern (as Dr. McDonough did in his presentation) over the consistency of findings between different laboratory-developed tests and how these LDTs compare to FDA-approved companion diagnostics (a key topic of discussion when GPC held a workshop on the clinical utility of next generation sequencing on July 7, 2014). Meanwhile, liquid vs. tissue biopsy concordance, or the significance and utility of proteomics, or (soon) microbial DNA analysis are overlain on these basic questions of sequencing consistency and quality. Even for the more established tissue-based gene panels for tumor profiling, a gap remains between the information the “front line” clinicians get and what they want (even as these types of products proliferate in the marketplace). In interpreting the results, genetic counselors clearly serve a critical role. Yet if, as Dr. Phurrough noted, most clinicians currently do not act on the test results received, then a significant gap exists between what payers pay for and what patients receive. The gap needs to be filled with better information and clinical evidence – something forward-looking health systems and initiatives such as the Cancer Genome Atlas seek to accomplish as quickly as possible.
Continued dialogue is needed for GPC to assure clarity on the evidence being produced for key decision-makers. Questions for deeper consideration include:

- What evidence will be needed for liquid biopsy testing to mature as a clinical tool and how will it best be used in patient care?
- How can innovative health systems share information and best practices in a way that will accelerate learning and ultimately benefit patients?
- Through what framework should payers assess the value of diagnostics?
- When might a “genomes for all” approach to medicine become mainstream, and under what circumstances would public and private payers see value in this approach?

The Genomics Technology Forum ended with a brief but far ranging discussion of issues that arose through the various presentations. Notably, there was a recognition of the interdependence of test and associated drug development. Those creating cancer genomics assays must increasingly understand the whole drug cost and practice ecosystem around their tests. There was a concern that the field needs to think about its language to manage patient expectations surrounding the “moonshot” promise of new technologies and targeted therapies. Finally, given the exciting work taking place in so many different places, there was a call for “convergence,” that is, for the field to develop a way for all stakeholders to understand who is doing what, and where the data repositories, tools, and best practices are. The hope looking ahead is to enable each group—payers, policymakers, industry, clinicians, and patients—to understand its role more clearly and to work together to move the field ahead, and the work of groups such as Green Park Collaborative can help to foster this understanding.