# DRAFT MEETING PROCEEDINGS

## Unifying the Evaluation and Implementation of Genomic Medicine

## August 18, 2016, Bethesda, MD

IGNITE (Implementing GeNomics In PracTicE) is an NIH-funded network dedicated to advancing genomic medicine in patient care. Initiated in 2013, the network comprises six research sites, a coordinating center, and six working groups. The research sites were tasked with finding ways to incorporate genomic information into electronic medical records and develop clinical decision support for providers across diverse healthcare settings. The IGNITE Network also disseminates the methods and best practices its members developed and tested in order to increase the use of genomic information in healthcare. One challenge to be addressed is that the rapidly evolving landscape of genetic and genomic testing combined with the diversity of payment models in the United States makes reimbursement decisions complex. The purpose of this meeting was to bring together stakeholders in these decisions to communicate with one another and begin a process to address this challenge.

Research Sites

Implementation, Adoption, and Utility of Family History in Diverse Care Settings
Principal Investigators: Geoffrey Ginsburg, MD PhD, and Lori A. Orlando, MD MHS
Duke University School of Medicine (coordinating center)

Genomic Medicine Implementation: The Personalized Medicine Program
Principal Investigator: Julie Johnson, PharmD, University of Florida College of Pharmacy

Genetic testing to Understand and Address Renal Disease Disparities: The GUARDD Study
Principal Investigator: Carol Horowitz, MD MPH
Mount Sinai, Icahn School of Medicine

Integrated, Individualized, Intelligent Prescribing ($I^3P$)
Principal Investigators: Joshua Denny, MS, MD, and Mia Levy, MD, PhD
Vanderbilt University School of Medicine

INdiana GENomics Implementation: an Opportunity for the UnderServed
Principal Investigators: Paul Dexter, MD, and Todd Skaar, PhD
Indiana University School of Medicine

Genomic Diagnosis and Individualized Therapy for Highly Penetrant Genetic Diabetes
Principal Investigators: Toni I. Pollin, MS, PhD
University of Maryland School of Medicine

**Working Groups**
Common Measures
Clinical Informatics
Clinical Validity, Utility and Economics
Provider Adoption, Barriers, and Education
Pharmacogenetics
Dissemination, Outreach, and Sustainability

Meeting attendees included members of the INGITE Network, representatives from payer organizations and biotechnology companies, patient advocates and other clinicians/scientists interested in this area. Toni I. Pollin, MS, PhD, IGNITE Steering Committee Chair, hosted the meeting.

**Welcome, Introductions, and Goals of Meeting**

Eric Green, MD, PhD, Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), provided the opening remarks for the meeting. He first gave an overview of the IGNITE Network citing that:

- The IGNITE Network is one of several NHGRI programs designed to promote the application of genomic technologies, particularly use of an individual's genetic variation, in clinical care.
- IGNITE focuses on dissemination of genomic approaches from highly specialized tertiary centers to diverse clinical settings, including primary care and resource-limited centers.
- Its multidisciplinary research touches many areas, such as institutional needs, clinical decision support, physician education and engagement, reimbursement and billing, and patient education and feedback of results.

Dr. Green noted that NHGRI recognizes how the cost of new technologies and improvement in patient outcomes are key determining factors in their adoption and reimbursement in clinical practice, and that IGNITE is designed to address these factors by exploring economic issues in genomic medicine within its individual studies and in the network as a whole.

He framed the purpose of the meeting, stating that in tracking the progress from bench to bedside, NIH and NHGRI see an inextricable relationship among research, evidence-based medicine, and health economics and reimbursement, and that this meeting is one of the many steps needed to engage various stakeholders--consumers, clinicians, laboratorians, regulatory entities, and third-party payers==in meaningful dialogue.

Toni Pollin, MS, PhD, (IGNITE Steering Committee Chair and Principal Investigator from the University of Maryland School of Medicine) and Daniel Mullins, PhD (health economist, and chair of the Department of Pharmaceutical Health Services Research (PHSR) at the University of Maryland School of Pharmacy) welcomed the attendees and provided the specific objectives for the meeting:

- To begin to build a process for communication among patients, providers, insurers, and researchers for a team-oriented approach to evaluating and implementing genomic medicine
- To understand what evidence is needed and how it should be disseminated for all
- To identify protocols that will help to provide evidence needed to make genomic medicine sustainable

Dr. Pollin re-emphasized the importance of bringing together stakeholders who would normally not communicate to have a conversation, recognizing the diverse agendas represented by the meeting participants, and how open, honest dialogue is needed for success. An antitrust policy statement was read to remind attendees that, any activity that intentionally or unintentionally reduces competition or restrain trade is contrary to the belief of the IGNITE Network.

Dr. Pollin concluded her remarks with an outline of the proposed next steps after the meeting:

- creating a formal proceedings document, and
- writing a manuscript based on the meeting that will be submitted to a peer-reviewed journal. We will solicit authors for the manuscript from the meeting attendees and list all attendees as contributors in the publication.

**Keynote Address, *The Future is Now***

*Speaker 1: John Brumsted, MD-- Chief Executive Officer of The University of Vermont Medical Center, President and CEO of The University of Vermont Health Network; practiced as an obstetrician/gynecologist and reproductive endocrinologist; first medical director of the Vermont Health Plan (the first managed care subsidiary of Blue Cross Blue Shields in the state).*

Dr. Brumsted spoke to the audience about how the leadership team at the University of Vermont Medical Center (UVMMC) and Health Network (UVMHN) is using the premise that, "providers, when given the accountability, make the best use of health care dollars," to guide them into a future where high quality care and financial accountability coexist. UVMHN's leadership team believes that the best way to effectively control health care cost in the long run is to make providers accountable for finances, medical decisions, and quality of care for patients and the communities they serve, and that genomic testing will be an integral tool for achieving that goal.

Dr. Brumsted recounted Vermont's journey toward an accountable care organization (ACO) model. UVMMC launched a strategy to develop an integrated delivery system in the large, rural geography that served a population of approximately one million people in northern New York and Vermont. The goal: implement an ACO that brings together all of the region's providers (particularly primary care) and hospitals under a shared infrastructure that could accept payments across the network.

Currently, the new, statewide ACO joins hundreds of health providers serving patients in the northern Vermont and northern New York region, and the leadership team is in the process of bringing global payment revenue into the provider-led ACO to distribute those funds to healthcare providers. In addition, UVMMC believes that this model provides several key benefits:

- incentivizes providers to focus on keeping people healthy,
- places priority on investing in the academic and clinical of telehealth missions, and
- emphasizes the centralization of administrative functions, such as human resources and information technology, to achieve significant economies of scale.

To conclude, Dr. Brumsted outlined the vision for how genomics will support UVMHN's overall mission for the ACO. UVMC's leadership is committed to continued investment in genomics, and they believe that the advancement and realization of using genomic information for clinical care will be a powerful way for the medical system to keep its population healthy while remaining financially sustainable

- From a quality perspective, genomics will drive accurate diagnosis, thereby serving as an underpinning of financial sustainability.
- The ultimate vision is that, at a particular age defined by stakeholders, the members of population that the medical system serves would all (at the primary care level) receive

their genome—and it would be socially acceptable. From those results, providers would develop a life-long health maintenance plan.

While UVMHN's leadership understands that implementing genetic testing as a standard will prove challenging, they are committed to continued investment in the area and collaboration with researchers and other stakeholders.

*Speaker 2: Josh Plavin, MD, Senior Medical Director, Blue Cross Blue Shield of Vermont* (BCBSVT*); independent Vermont based health plan that covers approximately a third of the Vermont population; manages the majority of commercial market in VT and over 90% of the VT "health exchange" market.*

Dr. Plavin presented an overview of BCBSVT's involvement in a Vermont provider and health plan research pilot for focused panels for tumors. The health system identified a rise in the use of large panels from outside labs, which had numbers of genes investigated in the realm of 350, many of which were of undetermined significance. Some of those tests were previously deemed investigational, and patients were at risk of being balance billed. However, providers were trying to give patients the best care, and the large panel genomic tests seemed to be the best option.

BCBSVT decided to collaborate with providers at the UVM Cancer Center to create a narrower gene panel for solid organ neoplasm (personalized tumor genomics). A desk procedure was implemented for coverage of CPT code 81445 (5-50 targeted genomic sequence analysis panel for solid organ neoplasm.) The prior authorization process was eliminated, and cost for the test was processed through the claims system for payment. They used the overall framework of the national BCBS Association Medical Policy Panel's guidelines for genetic panel testing for cancer:

- Test cancer cells from an individual to benefit the individual by identifying targeted treatment
- Most tests will not, and possibly should not, be ordered by generalists
- Many tests, particularly those for inherited disorders, should be accompanied by patient counseling, preferably by certified genetic counselors.
- Test is performed in a Clinical Laboratory Improvement Amendments (CLIA)–licensed Lab
- Analytic validity of panels should be close to that of direct sequencing
- The impact of ancillary information is well-defined
- Decision making based on genetic results Is well-defined, and the yield of testing is acceptable for the target population.

Dr. Plavin concluded that, within the movement toward population-based health care, providers and health plans have an exciting opportunity to build partnerships similar to the one between BCBSVT and UVMMC, thereby leveraging the expertise of both parties to benefit patients. Personalized genomics that drive targeted therapies for cancer may prove transformative in the area of cancer care, improving outcomes, patient experience, and the overall cost of care.

**Session 1: Targeted Genotyping**

*Speaker: Larisa Cavallari, PharmD, University of Florida Health (UFHealth)*

Dr. Cavallari provided background on UF Health's personalized medicine program (PMP), part of the Clinical Translational Science Institute, and presented a case study on screening for *CYP2C19* genetic variants in patients undergoing cardiac catheterization.

UF Health launched its PMP in June 2012 with the initial focus on testing to predict response to clopidogrel (Plavix) for patients undergoing percutaneous coronary intervention (angioplasty.) The PMP was established on several guiding principles:

- There is a regulatory body (PMP Committee) within the health system that reviews the evidence and defines pharmacogenetic examples as clinically actionable
- Must have clinical decision support tools built into the electronic medical record to assist physicians in interpreting and applying genetic test results to prescribing decisions
- Implementation efforts must be clinically realistic (need to take into account factors such as reimbursement for testing and the complexity of the process)

The eventual goal is to perform pre-emptive panel-based pharmacogenetic testing on multiple variants that have implications for multiple medications, which would overcome a major barrier that persists with reactive testing (ordering a test at the time a drug is prescribed) in that the results are available immediately to inform prescribing decisions. Right now, there is no means of reimbursement for panel based testing, so while it may be more logical, it is not clinically realistic.

Dr. Cavallari outlined the factors considered when implementing a genetic test:

- Is there consistent evidence that the genotype influences drug response?
- Is genotype information in the FDA-approved labeling for the drug?
- Are alternative drugs or dosing available for patients predicted to have a poor response to usual therapy?
- Are there guidelines to assist with translating the genetic test results into prescribing decisions?
- Is it reimbursed by the payer?

The *CYP2C19* testing for clopidogrel met all of the criteria, underpinning the decision to implement the test. An additional goal, because there are no clinical trial data currently available regarding the clinical utility of genotype-guided clopidogrel use, was to generate evidence for the utility and feasibility of genetic testing in a real-world setting.

Key facts about clopidogrel metabolism

- Clopidogrel is a prodrug, inactive when taken; it has to transformed by the body into its active form
- CYP2C19 is a key enzyme that activates clopidogrel
- Genetic variation of CYP2C19 interferes with activity of the enzyme that biotransforms clopidogrel
- Those with genetic variation leading to loss of enzyme activity cannot fully activate clopidogrel, and there is consistent evidence that such individuals are at risk for poor response to the drug.
- There are alternative drugs, prasugrel and ticagrelor, that are not affected by *CYP2C19* genotype, but are more expensive and associated with higher bleeding risk

Implementation

- Genetic testing for CYP2C19 was added as a standard or care for patients undergoing PCI (could be deselected by the physician.)
- Testing was done under clinical consent, so there was no additional consent needed.
- The *CYP2C19* genotype was placed in the patient's medical record, and clinical pharmacists followed up on all test results.
- In the event that the patient had a loss-of-function variant, the pharmacist followed up with the physician to recommend an alternative drug.
- Clinical decision support was built into the medical record so that if a physician attempted to prescribe clopidogrel in the future, an alert would trigger for patients with a loss-of-function variant warning of reduced clopidogrel effectiveness and recommending alternative therapy

Outcomes

- After the first two years, medical records were reviewed for patients who underwent PCI and genotyping during that time period (approximately 400 patients)
- Data were collected on Major Adverse Cardiovascular Events (MACE, defined as cardiovascular death, myocardial infarction, stroke, or stent thrombosis) through six following PCI
- MACE was compared between patients with a loss-of-function variant treated with alternate drugs and those with a loss-of-function variant treated with clopidogrel

Results (presented at the 2015 American Heart Association Scientific Sessions)

- There was a significantly lower risk for MACE in patients with a loss-of-function variant treated with alternative drugs compared to those with a loss-of-function variants treated with clopidogrel; most events in clopidogrel-treated patients occurred within first 30 days
- Testing for *CYP2C19* falls under the DRG, so the hospital had to make the coverage decision. The fact that most of the events occurred within the first 30 days of PCI provides support for hospital coverage of the test as a means of avoiding penalties for patient re-admittance for recurring events during the 30-day period following discharge.

As part of the IGNITE Pharmacogenetics Working Group, UF Health collaborated with the six other institutions where *CYP2C19* genotyping has been implemented clinically to examine outcomes in a larger patient population. Findings from approximately 1,800 patients were presented as a late breaking special report at the 2016 American Heart Association Scientific Sessions and confirmed previous findings at UF Health. An economic analysis of the real-world data derived from the collaborative is underway. Dr. Cavallari concluded with a question to payers: what kind of evidence is needed to cover pharmacogenetic tests?

*Speaker: Kathleen Palmer, RN, research coordinator for all* CYP2C19 *implementation studies at the University of Maryland Medical Center and Veterans Affairs VA Medical Center*

Ms. Palmer spoke on the patients' perspective of having genotyping performed during the Translational Pharmacogenetics Project. Although she was not a patient in the study, she coordinated enrollment for 75% of the approximately 600 people who participated. Funded by National Heart, Lung and Blood Institute (NHLBI), the research study took place between March 2013 and April 2015. The study started following Dr. Alan Shuldiner's study of clopidogrel response in an Amish population. The aim of the project was to evaluate the implementation of *CYP2C19* testing at the University of Maryland School of Medicine, a setting where clinicians rarely performed such testing; there had been approximately five tests ordered in the year prior to the research period.)

Population of Patients Enrolled in Research Study

- The patients enrolled in the study were all scheduled to undergo catheterization and were considered by their clinicians to have an indication for antiplatelet therapy following their catheterizations.
- Not all of patients were stented. Many were catheterized for diagnostic testing. Some where patients with acute coronary syndrome (ACS), STEMI and NSTEMI; a small number of participants were recruited after they received a stent.

Recruitment and Disclosure Process

- 771 people were approached to participate in the study. 667 were enrolled.
- Patients were approached in the prep center, where they had approximately 30 minutes to four hours before their catheterization procedure.
- Patients had to give informed consent.

In general, the patients were very receptive to hearing about the research study, and seemed to recognize that genomic medicine is trending in health care (although they had no prior knowledge of CYP2C19 in particular).) Patients who declined to participate cited reasons such as:

- Confidentiality concerns –most were concerned not with the actual genetic testing, but with people having access to their medical records (did not want genotyping results going into their medical record, or having the medical record accessed/reviewed one year after outcomes per the research protocol)
- Being too overwhelmed in the clinical setting to make a decision to participate
- Wanting to wait until after they received the catheterization to see if they'd need an antiplatelet agent.

The disclosure process was straightforward, but researchers found that there is an issue with disclosure when patients are hospitalized for fewer than 24 hours. All results included recommendations for further action or treatment, and researchers stressed the need for patients to carry the results through to other providers.

- Results were delivered to patients in person when possible. Otherwise, the test results were mailed.
- Patients were overwhelmingly pleased to have tangible results.
- Results were delivered to providers. In about 55% of the cases where there was an actionable result (i.e., intermediate or poor metabolizer for someone who was stented) providers changed patient therapy. Some providers did not change the patient's therapy because of bleeding risks associated with the alternative drug, age, complicated procedures, or concerns that the patient did not have adequate insurance coverage for the more expensive drug. Some patients with actionable results refused switching treatment.

**Discussion**

The ensuing discussion topics varied, with talking points that explored:

- pre-emptive *versus* reactive pharmacogenetic testing,
- benefits and challenges of genotyping,
- current policies/guidelines payers use to make payment decisions for genomic testing,

- clinical and medical utility,
- and ownership and access of genomic data.

While there was significant agreement among researchers, clinicians, payers, association members, and patients that there are benefits to both genotyping and phenotyping, the diversity of patient populations, provider preference, and varying resources among health care systems make it challenging to assert either as a clear best practice.

*Discussion point: who paid for CYP2C19 testing during the studies at participating institutions?*

Audience members questioned whether the *CYP2C19* testing was paid for by insurers or by the research project. Dr. Cavallari clarified that it was performed as clinical care, not a research project. Data were collected and analyzed, and testing was funded by institutional support and research dollars during the first year. This approach gives gave providers time to become familiar with the tests (i.e., how to order, what patients to order it for, how to act on results.) UFHealth began clinically billing in the second year, and Dr. Cavallari believes that the reimbursement rate was close to 90%. Since then, testing cost has been covered by the hospital because it falls under the DRG. At the University of Maryland, testing was paid for with research dollars, but the data from the TPP were being used to work on setting up clinical testing with billing to patients and payers.

*Discussion point: an attendee from a payer organization questioned whether testing was paid for based on actual evidentiary review, or simply because it fell below the baseline cost for review.*

UFHealth reviewed ICD9/10 data for relevance, but since the test for inpatients was covered by DRG, there was no payer engagement. For outpatients, payers agreed to pay based on CPT code for test.

*Discussion point: is pre-emptive pharmacogenetic testing better than reactive?*

There was significant discussion surrounding the benefits of performing genetic testing prior to a procedure or medical event (pre-emptive testing) or if testing during or after such an event was a feasible alternative. To this end, Dr. Cavallari was asked whether there were any data regarding the rate of stent recipient relapse or complications during the two-three day time frame between the sample collection and results. Is there a way to shorten the time to results, or is pre-emptive testing the only way to ensure that actionable information is received in time?

Dr. Cavallari confirmed that there were a few cases of cardiovascular events between the procedure and the time test results were reported. She explained that all genetic testing is considered high complexity, even though the procedure may be straightforward, meaning that it needs to be done in a CLIA licensed environment by appropriately licensed personnel. While there are point-of-care-style testing methods available for *CYP2C19* genotyping, logistics may prevent the use of such tests in clinical care, as would be the case with UFHealth, because the sample must be tested within an hour of collection. If the CLIA licensed laboratory is not located near the patient, the test cannot be completed within the hour.

Dr. Marc Williams, a genomic medicine implementation researcher, expanded on the idea that genetic testing can be straightforward, even though always classified as high complexity, using an example of health workers in Africa who received minimal training performing such tests for malaria and ebola, garnering highly-reliable results in less-than-ideal clinical settings. He

believed that a more pressing question is whether the FDA would choose to exempt genomic testing as high-complexity to allow single-gene testing.

He concluded that the duplication of testing, whether pre-emptive or reactive, created a larger issue from a payer's perspective. He cited his own study where 5% of the genomic testing performed within Intermountain Healthcare, Dr. Williams's prior affiliation, had been previously done. This was consistent with a published study from the Mayo Clinic that showed a similar rate of duplicate genetic testing. He shared concern that, if genetic tests are unnecessarily repeated within a single health system, they certainly will be duplicated as patients switch systems. He concluded that, in an ideal world, germline genomic testing that can be used for payers to make evidence-based decisions be performed once and made available for the rest of the patient's life.

From a researcher's view, there was also agreement that, in an ideal world, genetic testing should not be repeated. However, one researcher suggested that continued advances in technology, as well as knowledge gained from future research, may make future genomics testing necessary.

*Discussion point: why is it easier for insurers to make a payment decision for CYP2C19 testing as opposed to other tests? How does clinical utility and medical necessity factor into the payer decision-making process?*

Payers, providers, and association members offered varying insights to answer why it seems easier to make a decision to pay for a test like *CYP2C19* as opposed to other genetic tests. A key factor in the decision-making process that is not usually considered by providers and patients is that many insurers do not create their own medical guidelines. In most cases, medical guidelines used to make payment determinations are generally put forth by larger insurers and are often adopted intact by others. There are also commercial entities that develop medical guidelines. Internal guidelines may or may not be developed for highly-technical testing like genetic testing. An individual medical director may deem a test medically appropriate, but the guidelines that payers must use may not support the medical director's determination.

A payer noted that, while it is true that policies are relatively standard, science evolves, which causes health plans to also evolve. He also emphasized that policies are guidelines that cover the majority of situations, but that medical necessity ultimately comes down to the individual patient. There is always room for policies to evolve.

As an example of disparity within the payer industry, another payer told the group that they do not pay for *CYP2C19* testing. They go through the same review process as other payers, but their cardiologists prefer to perform platelet testing. Therefore, this payer concluded, neither clinical or economic utility was established for their particular system. A researcher explained the difference between genotype and phenotype (platelet function) testing genotype testing can, ideally, be ideally performed before the drug is prescribed, so that it can inform whether the person should actually be on the drug. Phenotype testing requires the person to already be on the drug. Cardiologists may prefer platelet testing because they more easily understand the results and their actionability.

A representative from the Blue Cross Blue Shield National Association provided key insights regarding evidence utilization and medical necessity. There was agreement that there is significant overlap between evidence utilized to create local decisions in regards to what test to

cover. She stated that the Association believes that all of the decisions regarding medical necessity requirements should be made locally, and that evidence review is often just one portion of making an individual coverage decision. Also, it was suggested that the industry could do a better job of creating a common evidence base that has inputs from all relevant stakeholders so that, collectively, all of the information required to make an best evidence review for any intervention can be accessed and utilized by health care decision makers across the country to make a local decision while using a standard set of evidence reviews that all stakeholders agree upon.

A researcher explained the difference between genotype and phenotype (platelet function) testing—genotype testing can, ideally, be performed before the drug is prescribed, ideally, so that it can inform whether the person should actually be on the drug. Phenotype testing requires the person to already be on the drug. Cardiologists may prefer platelet testing because they more easily understand the results and their actionability.

A health system executive asserted that, while all health plans are required to perform the same kind of reviews, there are smaller plans that lack the resources to do it, and they adopt others' policies or choose to exclude particular categories of testing. In fact, excluding genetic testing is common. Therefore, when it is not a covered benefit, the evidence is irrelevant. He also explained that medical necessity is subjective, which makes it hard for both researchers and payers; groups interested in generating evidence that is of use to health plans should ask what is the specific type of evidence that would be most compelling for payers to make decisions. In addition, choosing to pay for genotyping versus phenotyping is not just a matter of cost, but also must be supported by how the choice to perform either type of testing may affect the overall cost of care. Socioeconomic variables which differ among patient populations must also be considered.

From the association perspective, coverage review and evidence review are two different things. Also, clinical utility from their perspective should be evaluated and defined by whether there's an improvement in net health outcomes—does using the test improve net health outcomes for the individual being tested, or a group of individuals in the same circumstance. There are direct and indirect paths for assessing clinical utility. Direct would mean randomized, controlled trials, while the indirect path, used more frequently, often hinges heavily on the fact that there is very strong evidence for the analytic validity of the test. Historically, across the evidence review landscape, there has been very little attention paid to the assessment around the analytic validity of a test. The growth in the number of companies that assess genetic test is making it even more crucial to create standards and make them transparent.

## Session 2: Targeted sequencing panel-based genetic testing

*Speaker: Toni Pollin, MS, PhD, University of Maryland, School of Medicine*

Dr. Pollin spoke about monogenic diabetes, caused by a mutation in a single gene and accounting for at least 1-2% of diabetes. In contrast to the polygenic diabetes types 1 and 2, there is clear clinical utility for genetic testing in monogenic diabetes, particularly for neonatal diabetes and the subcategory known as maturity-onset diabetes of the young (MODY) or transcription factor/glucokinase (GCK) diabetes.

- Neonatal diabetes (occurring before 6 months of age) is rare (~1/100,000) and may be permanent or transient. About half of permanent cases are caused by mutations in the two genes encoding a ATP-sensitive potassium channel; most of these cases can be treated with high dose oral agents in the sulfonylurea class, resulting in safer and more efficacious glucose control.
- MODY accounts for most monogenic diabetes and occurs in older children and young adults, but sometimes not diagnosed until later adulthood. The most common forms of transcription factor MODY, caused by mutations in *HNF1A* and *HNF4A*, can usually be successfully treated with low dose sulfonylureas rather than insulin, especially early in the disease progression. GCK-MODY is characterized by lifelong stably elevated fasting glucose that usually does not require treatment to prevent complications.
- Misdiagnosis of these forms of monogenic diabetes leads to unnecessary and sometimes dangerous insulin use with the misdiagnosis is type 1 diabetes and use of insulin-sensitizing drugs when the misdiagnosis is type 2 diabetes that are unlikely to be efficacious.
- Data from the SEARCH study, an epidemiological study of childhood diabetes, provide evidence that monogenic diabetes is misdiagnosed as other types of diabetes over 90% of the time.
- Barriers to a correct diagnosis include lack of awareness, cost and complexity of testing, clinical overlap with other forms of diabetes, notion that “rare means never,” and the life-changing vs. immediate life-saving nature of getting a correct diagnosis.
- Dr. Pollin and her team designed the Personalized Diabetes Medicine Program, an IGNITE project, to implement, disseminate and evaluate a comprehensive approach to the detection, molecular diagnosis, and promotion of individualized therapy of monogenic diabetes. The approach includes a simple screening questionnaire, an in-house 40 gene NGS panel performed on a research basis, CLIA confirmation and disclosure to patients and providers/EHR of pathogenic and likely pathogenic variants and their clinical implications. Effects of a molecular diagnosis on clinical (glycemic) outcomes, service utilization and patient reported outcomes are being evaluated, and payers are engaged in discussions.
- To date they have diagnosed several patients with monogenic diabetes, mostly GCK-MODY (MODY2).

*Speaker: Jennifer Rice, MBA, Patient Advocate*

Ms. Rice recounted her journey through several misdiagnoses to a diagnosis of *GCK*-MODY/ MODY2, and the critical role that genetic testing played in reaching that outcome. In 2005, at the age of 36 and during pregnancy with her first child, a routine glucose tolerance test showed an abnormal result. She was diagnosed with gestational diabetes and put on insulin. After delivery, her hyperglycemia remained and insulin was continued. Her physician could not figure it out, as her condition didn't fit with any of the known types of diabetes. However, she was told to remain on insulin to prevent complications and was put on an insulin pump after delivery. After her second pregnancy, her glucose was so close to normal that it would have been dangerous to put her on insulin again. She remained off and stayed off for several years. To further complicate her medical care, she relocated to a different state and went under the care of a new primary care physician who at one point diagnosed her with type 2 diabetes.

In 2013, a different endocrinologist again diagnosed Jennifer with type 1 diabetes and she was put back on insulin. Nearly a year later, he told her he questioned her type 1 diagnosis as she entered the care of a third endocrinologist who also questioned her diagnosis and, after working with Jennifer for a year, suspected she had a rare genetic type of diabetes. He strongly

encouraged her to undergo genetic testing to determine if her condition was MODY 1, 2, or 3. The testing, however, was also a financial decision. Even if insurance covered the cost, it was estimated to cost $1200-$2000 out-of-pocket. However, after several months of consideration, Jennifer had the test performed. The genetic test results revealed a pathogenic mutation in GCK. Her type 1 diagnosis was changed to MODY2, and her new prognosis of no complications resulted in the end of Jennifer's insulin regimen, as it is usually not needed and fails to normalize glucose levels in people with *GCK* mutations.

It was also noted that, during the 10-year period with varying diagnosis and treatment, Ms. Rice's insurance company paid for repeat testing and doctor's visits, including visits to specialists like podiatrists and neurologists, all in an effort to treat and prevent complications from a disease that, ultimately, she did not have. She concluded with an imperative that genetic testing be made more accessible so that other patients don't have to experience what she did on her search for the proper diagnosis and treatment.

**Discussion**

*Discussion point: clinical utility and value, specifically how they are defined and evaluated, for targeted sequencing panel-based genetic testing*

The first comment was that the example of MODY to illustrate the benefits and clinical utility of genetic testing is a best-case scenario, as there is significant clear evidence that genetic testing makes a dramatic difference in the outcome and in the treatment management for the affected person. That knowledge makes for easy decisions. They become much more difficult when the evidence is not so compelling.

The moderator posed a question to the payers: What level of evidence do you require to assess clinical utility? Does it need to be a randomized clinical trial or are you willing to accept other types of evidence, particularly for those tests not as clear as the MODY?

The first response came from a representative of a large payer organization. She stated that the type of evidence necessary depends on the situation. For example, if there's a condition which is of reasonable prevalence and there is a professional organization that is respected that makes statements based on evidence, their guidelines are usually taken seriously. Conversely, evidence and opinions on testing and treatment from professional groups that are thought to be "self-serving, generally, are not going to be considered as convincing. There may not necessarily have to be results from a randomized clinical trial if there are professional societies that have made reasoned statements on evidence or if there is overwhelming clinical information that would suggest a particular kind of test is appropriate. The evidence needed also depends on how common the condition is, the severity of possible complications, alternatives to a particular test, as well as the cost of the testing.

Another payer added that, while it may be easier to assess clinical utility and value--and subsequently whether to pay for testing--on an individual basis, the larger challenge is the systemic application of the guidelines that will ultimately affect premiums and coverages.

A representative from a small, regional payer organization offered another perspective on clinical evidence and utility. While both large and small payers share the desire for adequate clinical evidence, RCTs have their limits. They don't take into account real-world environments, for example, variations in patient compliance in larger urban areas versus rural areas. Those variables impact cost, therefore, making it critical to include economic analysis instead of solely relying on RCTs to make decisions. Smaller systems have to pay close attention not just to the

clinical utility for one or two patients, but for the economic utility of allowing a particular testing or technology across an entire covered population.

Jennifer Rice, a patient advocate, provided further details about her experience, noting that her insurance company would not pre-certify her testing. However, she ultimately incurred no out-of-pocket expense for the genetic testing that lead to her MODY2 diagnosis. She posed a follow-up question to the payers: why can't individual cases, particularly dramatic ones like hers, be considered sufficient evidence for approving payment for a test?

A payer representative responded that the people who make coverage decisions have varied experience levels and different supporting resources available to them. However, when it comes down to the actual processing of a request, the people reviewing the evidence may not have a clear and concise research presentation in front of them. They may have few guidelines to follow, forcing them to interpret the way the evidence is presented based on limited information.

The payer representative further explained that the review process with most payers allows patients to request a second look or a third review if the benefit is initially denied. And oftentimes in those second or third reviews, which are either reconsiderations or repeals, there's an opportunity to provide additional evidence and hopefully to make a better decision with a stronger basis than the first.  can be made whether it be the same one as the first a decision or a change.

Also discussed was the severe shortage of genetic specialists and genetically-trained staff available within the payer organizations. The nurses and physicians making the initial coverage decisions rarely have training on genetics or molecular biology. External vendors are used to provide specialty reviews and additional expertise, but often only at the second or third-level review stage. The lack of training and expertise within payer organizations, as well as human error, such as coding mistakes when submitting requests for genetic testing, will continue to influence disconnects among patients, payers, and providers.

**Session 3: Genome-wide methods (arrays, exome, genome): Shifting paradigms**

*Speaker: Marc S. Williams, MD, Geisinger Health System*

Dr. Williams's presentation topic was obtaining coverage for genome-wide next generation sequencing, whole exome sequencing in particular. He began by comparing the clinical perspective with the payer/health system perspective (having worked on both sides has given him a broader perspective.)

From the clinical perspective, the value of whole exome/genome sequencing is:

- it increases our diagnostic yield,
- It supplants other testing,
- It shortens the diagnostic odyssey, and
- It empowers patients and families.

From the payer system perspective, whole exome sequencing:

- increases cost ,
- is yet another add-on technology,
- does not impact the diagnostic odyssey in a way that can be quantified

- payers don't pay for empowerment, and
- it doesn't change care.

He then outlined the evidence his team used to make the case to their provider-owned payer for covering whole-exome sequencing (WES). The evidence included:

- A statement approved by the American College of Medical Genetics and Genomics (ACMG) in May of 2012, which asserts "that there are already instances in which genomic sequencing approaches can and should contribute to clinical care."
- A March 2015 position statement from the ACMG: " …We submit that the clinical utility of genetic testing and services should take into account effects on diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and economic impact on health-care systems. We believe that clinical utility must also take into account the value a diagnosis can bring to the individual, the family, and society in general…"
- A paper published in JAMA in December 2014 regarding the effectiveness of exome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders.
    - Cost of prior negative tests in the non-acute patients was $19,100/family, suggesting whole exome sequencing to be cost-effective at up to $7,640/family
    - 49% had a change in clinical care
    - If WES performed at symptom onset, genomic diagnoses would have been made 6.4 years earlier than in this study

He also presented data that illustrated the difficulty of being the "new kid on the block" as the new technology as opposed to more established diagnostic tests, where payers tend to be more accepting in their utilization. His team found that, within the pediatric population, brain MRIs (a more established diagnostic tool that payers routinely cover) cost $6000, had a diagnostic yield of approximately 5%, and for the majority of the cases examined, prompted no change in medical management if a diagnosis was established. In comparison, WES, which cost $5000, resulted in a diagnostic yield of 25%-30%, and resulted in changed medical management for 30%-50% of the cases where a diagnosis was established.

Dr. Williams's team succeeded in convincing the payer to cover WES using the criteria for coverage they established. He concluded that:

- Genomics as an emerging technology must be able to demonstrate utility and ultimately improved value in the health care delivery setting before it will be adopted.

- Making the case for utility is complex and requires a systematic approach of engagement, education, evidence and evaluation.

- Outcomes must be defined and systems built to support measurement to determine which services have utility and add value.

*Speaker: Debra G.B. Leonard, M.D., Ph.D., Chair & Professor, Department of Pathology & Laboratory Medicine, University of Vermont (UVM) Larner College of Medicine & UVM Health Network (UVMHN)*

Dr. Leonard spoke about UVMHN's vision of "genome for all", based on the premise that genotype drives phenotype, and that genome provides fundamental medical information for every patient. The institution's hypothesis for genomic medicine is that clinical genomics will:

- improve clinical care and the health of our patients through improving patient outcomes,
- increase cost-effectiveness, and
- potentially drive disease prevention and enhance disease monitoring capabilities.

She asserted that, although a person's genome doesn't reveal everything, neither do height, weight, blood pressure, or heart rate—all of which are common pieces of information collected during each patient visit. However, the health care provider interpretation of a genome cannot be done simply by the information in the electronic health record (EHR). A patient's genome is part of what makes each person unique, while the patient's medical phenotype is seen by the health care provider and described, to some extent, in the EHR. She noted that, oftentimes, patients know more about their medical phenotype than the health care provider or what's documented in the EHR, making it necessary to combine both information sets (genotype and phenotype), along with close involvement and participation from the patient, to achieve the best, most cost-effective care.

*"A genome is a journey. It's something you do with a patient. And then as our medical knowledge increases and as you explore what you're seeing in the genome with the patient with what's in the E.H.R. you can use that information over time. So unlike other tests that you do once, you look at the result, and you file it away, you actually will go back to that genome over and over, [over] the lifetime of an individual."*

Because an accurate diagnosis has been proven to drive effective treatment, Dr. Leonard described how genomics can increase care provider's diagnostic ability. Healthcare provider diagnostic ability is limited by their knowledge-base, their biases (gender, race, age, etc.), and time. A genome may reduce diagnostic limitations by allowing providers to consider alternative diagnoses not limited by their biases or solely based on information in the EHR. A genome may also identify disease risks before onset of symptoms, allowing for targeted monitoring but only for at-risk individuals. Dr. Leonard gave an example:

"…I'm imagining a world where everyone has their genome. We would only be doing colonoscopies in those patients who are at higher risk, potentially. It could allow preventive strategies when those are available."

Next, Dr. Leonard provided an overview of UVMHN's current approach to genomics. They have implemented a full genomic medicine program to:

- Improve health and healthcare
- Drive genomic value & implementation research
- Provide genomic medicine education

*Speaker: Greg Merhar, Patient Advocate*

Mr. Merhar spoke about his experience with having his genome sequenced, and how genotyping proved more valuable than his phenotype and other diagnostic tests in identifying the cause of an illness he suffered from for his entire adult life: Familial Mediterranean Fever (FMF). In 2015, he and his wife paid $5000 each, out-of-pocket, to have their genomes sequenced through a program at Illumina called Understand Your Genome(UYG). They travelled to Vancouver, BC to receive the results at the UYG symposium.

While he characterizes his initial reaction to the results as boring, he found that he had three variants of unknown significance, but suspicious (VUSS).

*"But what caught my eye was the third VUSS – Familial Mediterranean Fever. And in reading the description that we got in the clinical report…at the top it says it involves recurrent episodes of painful inflammation in the abdomen, chest, or joints. And for as long as I can remember, probably from my late teens into the 20s, I have had pretty awful episodes of abdominal pain. I liken it to swallowing a basketball and having this basketball kind of just roll around inside of my torso and my upper half of my body for six to eight hours, generally happens at night. And then for some reason it just goes away."*

After conducting more research, he found that FMF is a very treatable disease. Colchicine (a very common gout medication) when taken regularly can almost eliminate FMF. He also found that a short trial of colchicine has long-since been used as a diagnostic tool for ruling in or ruling out a diagnosis FMF, since its only other known use is the treatment of gout.

During another acute inflammatory episode, Mr. Merhar went to see a rheumatologist. Armed with screenshots from his genome sequence, as well as research regarding the treatment for FMF (Colchicine,) he was ultimately able to convince the specialist to prescribe a 15-day trial of the medication. Positive results were immediate, and Mr. Merhar has since been officially diagnosed with FMF. Although his primary care physician knew about FMF and was currently treating four other patients, he did not consider the diagnosis for Mr. Merhar because he has blonde hair and blue eyes. FMF predominantly effects people in the Mediterranean basin—Turks, Armenians, Ashkenazi and Sephardic Jews -- basically dark haired and dark eyed people. He concluded that having his genome sequenced was a life-changing experience, and could have prevented decades of pain and suffering.

**Discussion**

*Discussion point: how to define clinical utility, value, and outcomes*

The discussion began with a health system representative providing that organization's definition of outcomes. He separated them into two general categories: health outcomes and service outcomes. He characterizes health outcomes with measures such as development of disease, treatment of a disease, along with the length, effectiveness, and cost of diagnosis of treatment. Examples of service outcome measures included how many times a patient has to return to a doctor for a diagnosis, how onerous the treatment is, and whether the patient feels satisfied and empowered after the diagnosis and treatment. He also identified process outcomes and intermediate outcomes to deal with long-term and/or chronic illnesses like hyperlipidemia. He concluded that all outcomes have to be considered from the patient perspective because the patient is the only constant actor in the healthcare delivery system, and if payers and clinicians don't think about outcomes from that patient perspective then ultimately they're not measuring properly.

Another attendee commented that, in her organization, there is no medical necessity determination unless the case of clinical utility has first been proven. The previous payer offered that, while clinical utility is the predominant unit of measure among payers "medical necessity and clinical utility can be viewed as different sides of the same coin." He also noted that payers and clinicians define clinical utility differently, with clinicians believing that if it impacts the patient's health outcome, there's proof of clinical utility. Conversely, payers usually consider cost as an equal part in the clinical utility equation. The speaker added that genomics, with the vast

number of unanswered questions in both the clinical and payer communities, only increases the divergence of thought processes when determining clinical utility.

**Lunchtime Roundtables**

During lunch, the group was split up into several roundtables around the following themes and key points:

- Building a coalition
    - Is there a need?
    - What is the mission?
        - Address provider education? Standardizing panels?
    - How is it funded?
    - Can it be built on an existing organization(s)?
    - Who are the stakeholders?
    - Need active participation by payers, but payers don't have the resources to drive it.
- Evidence needed
    - Need more evidence on downstream costs
    - Role of guideline setting organizations
    - Need to publish evidence
    - Large payers gather their own evidence
    - Diagnostics manufacturers can support studies to generate evidence
    - Different perspectives on how "change in care" is defined
- Designing research/clinical protocols
    - Importance of study design and consideration of numbers
    - Should include but not solely focus on economics
    - Work with payers upfront
    - Important to look at diagnosis not as an end but how it affects patient care
- Disseminating evidence
    - Need for a central database
    - Need for a letter of medical necessity clearinghouse
    - A regular newsletter updating key advance would be useful
    - Medicaid takes input from patients and advocacy groups
    - Payers attend national professional/scientific meetings, another good outlet

**Summary of Key Observations**

- Coverage models are needed for human and bioinformatics resources as well as communication and explanation of results in addition to cost of testing
- Coverage models are needed for re-analysis of results from genomic tests (including not just previously identified variants and genes but additional genes as in the case of whole genome sequencing) and transporting those results when patients move into a different healthcare system, particularly as universal genome sequencing becomes closer to reality
- There are challenges in developing economic models that account for benefits and outcomes of genomic testing outside the purview of the entities providing care to the patient, including testing of family members, family planning, and getting a diagnosis to inform educational plans for children with special needs

- Models are needed for providing updated information on genomic service utility to payers
- Specificity of CPT codes so it is clear which test is being performed
- Role and value of whole genome sequence as an ongoing resource to inform diagnosis and treatment
- Defining clinical utility beyond effects on medical management
- Panel standardization