Rapporteur: Ian Marpuri
Program Analyst, NHGRI

Genomic Medicine Centers Meeting II
December 5-6, 2011
Hyatt Regency Bethesda

Attending

Baylor	Reid Sutton
Cleveland Clinic	Charis Eng
Geisinger	Andy Faucett
Geisinger	David Ledbetter
Geisinger	Joanne Wade
Johns Hopkins	David Valle
Marshfield Clinic	Murray Brilliant
Marshfield Clinic	Humberto Vidaillet
Mayo Clinic	Liewei Wang
Mayo Clinic	Dick Weinshilboum
MCW	David Dimmock
MCW	Howard Jacob
Morehouse	Adam Davis
Morehouse	Gary Gibbons
Mt. Sinai	Erwin Bottinger
NCI	Andy Freedman
NHLBI	Cashell Jaquish
NHLBI	Dina Paltoo
NHGRI	Les Biesecker
NHGRI	Lisa Brooks
NHGRI	Praveen Cherukuri
NHGRI	Greg Feero
NHGRI	Elise Feingold
NHGRI	Adam Felsenfeld
NHGRI	Bill Gahl
NHGRI	Peter Good
NHGRI	Bettie Graham
NHGRI	Mark Guyer
NHGRI	Rongling Li
NHGRI	Ian Marpuri
NHGRI	Jane Peterson
NHGRI	Rudy Pozzatti
NHGRI	Laura Lyman Rodriguez
NHGRI	Jeff Schloss
NHGRI	Jeff Struewing
NHGRI	Simona Volpi
NIGMS	Rochelle Long
NIMH	David Chambers
Northwestern	Mark Graves
Northwestern	Peter Kopp
Northwestern	Maureen Smith
Ohio State	Murugu Manickam
Partners Healthcare	Michael Murray
Partners HealthCare	Scott Weiss
St. Jude's	Bill Evans
Scripps	Eric Topol
TGen	David Craig
UAB	Jonas Almeida
UCSD	Kelly Frazer
UCSD	Richard Schwab
UChicago	Nancy Cox
UChicago	Peter O'Donnell
UChicago	Mark Ratain
UMaryland	Scott Devine
UMaryland	Alan Shuldiner
UNC	Howard McLeod
UPenn	Kate Nathanson
UWashington	Gail Jarvik
UWashington	Debbie Nickerson
Vanderbilt	Josh Denny
VA	Suma Muralidhar
VA	Maren Scheuner

NHGRI Genomic Medicine WG

Northwestern	Rex Chisholm
Duke	Geoff Ginsburg
NHGRI	Eric Green
NHGRI	Teri Manolio
Partners Healthcare	Pearl O'Rourke
NHGRI	Brad Ozenberger
St. Jude's	Mary Relling
Vanderbilt	Dan Roden
Intermountain	Marc Williams

Rex Chisholm- Welcome and Overview

Rex introduced the main goals of the meeting, which were to develop ideas for multicenter collaborative projects in translational medicine, to learn about new projects going on at other genomic medicine institutes, to identify infrastructure needs and possible solutions for the adoption of genomic medicine, and to share best practices. We will also learn about recent discussions of useful databases for genomic variants in the ClinVar/ClinAction space.

Eric Green- Remarks from NHGRI Director

Eric stated that this meeting serves to stimulate discussion and strategic thinking. In genomic medicine, NHGRI is currently working, among other things, on newborn screening, definitions of actionability and its implementation, and sickle cell disease. The scientific community looks to NHGRI to provide strategic advice, particularly for genomic applications and disease-specific aspects. Many genomic medicine experts at this meeting are also part of NHGRI's advisory panels. At the last Council meeting, NHGRI established the Genomic Medicine working group to carry out workshops and meetings like this. At this particular meeting, we need to be conveners, we need to be smarter with our resources, and we need to be matchmakers between the different institutes.

Geoff Ginsburg and Teri Manolio- Summary of Genomic Medicine I Meeting

Geoff and Teri presented about the first Genomic Medicine meeting held in Chicago in June. The meeting arose because of NHGRI discussions about its strategic plan and figuring out how to move genomic medicine forward. The tentative tasks of that meeting were to identify areas of active translational and implementation research across various groups and determine potential commonalities and uniqueness to show the value of translational genomics. Attendees filled out surveys related to their institution's program and answered questions about barriers to clinical adoption of genomic medicine at their institution, solutions to those barriers, and the role that NHGRI could play in order to facilitate genomic medicine implementation. Barriers included acceptance by institutional leadership and physicians, CLIA regulations, education, EMR integration of results, consent, and counseling. Possible outcomes from the meeting were an enhanced appreciation of genomic medicine efforts, the creation of writing groups for perspectives papers and best practices, planning groups for workshops or conferences, and a consortium for collaboration. Currently, one paper is in draft stages. The Genomic Medicine WG was formed to develop topics for subsequent meetings, white papers, and overall progress. Other related efforts include ClinVar, eMERGE, Clinical Sequencing RFAs, trans-NIH dissemination and implementation group, and the CTSAs. The previous ClinAction meeting discussed databases and actionable variants, this meeting hopes to discuss low-cost collaborative demonstration projects, and the May meeting will hopefully discuss standardization and quality control of genomic testing and reporting.

Marc Williams- Clinically Actionable Variants Meeting Summary

Marc discussed the results of the "Characterizing and Displaying Genetic Variants for Clinical Action" meeting, held as a collaboration between NHGRI and the Wellcome Trust. The goal of the meeting was to consider processes, databases, and other resources needed to identify clinically relevant variants, decide whether they are actionable and what the action would be, and provide information for clinical use. With so much data coming out of GWAS and sequencing studies, systematic collection, synthesis, and evaluation of these data are needed. It is critical to obtain consensus on what variants are

actionable and what actions can be taken. This information also needs to be available to clinicians through EMRs. Many previous meetings have concluded that we need a resource of this nature. Current resources (ClinVar and Ensembl) need annotation and updating functions, as well as data from diverse populations. Annotation is particularly important for variants of unknown significance (VUS), but researchers will most likely have to do this themselves. Somatic variation and very rare variation should also be included, as should measures of utility like PPV and penetrance. Decision-support tools will also need to be created for EMR integration. For criteria to consider something actionable, they debated whether they should focus on validity or go ahead and bin variants into levels of actionability. We need to have processes for binning variants and for classifying a VUS as pathogenic. Scalability will also be an issue, so they will need to figure out bins with no validity and also treat VUS as benign until found to be pathogenic. During this discussion, there was a clear divide between clinicians who need to make immediate decisions and laboratorians who can wait for more data. For EMR integration, we need to develop decision-support, access rights, privacy, and standards (like HL7) to aggregate data from multiple sources. This resource would sit on top of other resources like ClinVar and add annotation capability. ClinAction curation needs a function to build on existing resources, allowing many other types of researchers to obtain information on clinical validity and utility. We could also do long-term studies of patients with rare variants to understand the variants' relationships with phenotype. Patient portals seem especially important for patients to have data access. Return of results is also critical. The signature project developed is to feed WGS into software to produce a concise report regarding relevant genomic variants for a particular patient. This would allow testing of CDSS models and education tools as well. They recommended that the Genomic Medicine WG provide input as the database is developed. Three members of the ClinAction group will also be at the NIH Dissemination and Implementation group.

Participants discussed differences between actionability and clinical validity and utility. They also mentioned involving the Center for Medicare and Medicaid Services (CMS), which currently does not pay for preventive interventions. They also recommended creation of a centralized resource that can aggregate data from places like TCGA or ISCA CNV database and determine associations between rare variants and phenotypes. Clinicians also need access to information from proprietary labs like Myriad and Athena. The group could also work with the Office for Human Research Protections (OHRP) to determine the research/clinical care divide.

Institutional Leadership Perspectives on Implementing Genomic Medicine Programs

Bill Evans- CEO, St. Jude's

Bill Evans has been the director of St. Jude's since 2004. Genomics has been used at St. Jude's since 1984. They started adjusting TPMT therapy based on genetic polymorphisms with great success. There are now guidelines through the Clinical Pharmacogenetics Implementation Consortium (CPIC), but TPMT testing is still not routinely used because of skepticism in the medical community. It is now in the strategic plan to individualize therapy for patients and to become a model center for translating biological discoveries into treatments, as well as to find evidence-based decision support tools. In the TPMT case, pharmacogenomics genotypes that are clearly validated and of potential utility go onto the problem list in the EMR. Decision-support tools then alert the physician they should modify their prescription. Standardized language and alerts have been very useful. Genomics studies that are ready for the clinic need translational pieces, such as working with PharmGKB. General barriers to genomic medicine integration are fragmentation of the health care system, a lack of focus on prevention, modest evidence of clinical utility and cost-effectiveness combined with excessive high requirements,

complexity of lab results, and lack of use of decision-support tools. At St. Jude's, there are fewer barriers because it covers all patient costs, provides all medications, and tracks its patients regardless of location thanks to a multidisciplinary team with a comprehensive EMR. They use the DMET array as they start moving TPMT and CYP2D6 from the research to clinical side. Proper evidence allows the migration of these genes into the decision-support system. Broad consent in the PG4KDS program aids this process. The process is in a CLIA environment, but there still needs to be a process for withholding results and incidental findings. Findings are currently delivered to clinicians, and patients and parents can opt to receive a personal letter with genotyping results and metabolizer category. A family advisory council also helps develop trials. As they move forward, they are trying to figure out how to move more genes across the firewall, especially as they study the full scope of pediatric cancers and generate 2-4 WGS/day. In the next 10 years, WGS will be more affordable and PGx traits will be expanded for rare variants and polygenic interactions. Staff will also be more educated and trained to do this implementation.

Participants discussed that executive boards often like being innovative, but don't like to commit resources. Most primary treatment at St. Jude's is driven by research protocols. Patient outcomes are being tracked to see if protocols are followed, and clinicians are coached if the alerts are not followed.

Joanne Wade, Executive VP, Geisinger Strategic Program Development

Geisinger seeks to enhance quality of life through integrated health service based on a balanced of program of patient care, education, research, and community. Every 5 years, Glenn Steele, CEO of Geisinger, makes a new long-range financial model. There are a number of provider campuses, including a clinical center and ambulatory clinic. The research enterprise is part of the clinical enterprise and has over 300 FTE staff. Roughly 30% of business comes from the Geisinger Health Plan, and clinical care providers can be found in 43/67 counties in Pennsylvania. The demographic is an older homogeneous population, with most living in their homes for over 30 years. The EMR started in 1995 in ambulatory settings. It is integrated in all hospitals and community sites. There is now a portal for physicians who refer to Geisinger so that they can access patient records. They are trying to reach 200,000 portal users in addition to their 500,000 active consented users in the data warehouse. The MyCode program is a voluntary patient program seeking to create a biobank of a variety of samples. Real-time CDIS also supports this. The research strategic vision emphasizes personalized health care with an emphasis on genomics coupled with an innovative clinical provider system and payer. Three Geisinger board members have been involved in the development of this program. Many considerations were made in the approval progress, including risk mitigation, capacity, quality metrics, and proper leadership. Leadership and commitment at multiple levels have been very critical to drive this vision of demonstrating improved patient quality outcomes and improved value. Participants discussed tracking clinical outcomes and how RCTs are not as amenable to these sort of studies.

Potential Collaborative Opportunities

Charis Eng- Colorectal, neuroendocrine, and endometrial cancers

Charis presented on routine screening for neuroendocrine tumors, particularly pheochromocytomas (PC) and paragangliomas (PGL). Approximately 20-30% of all pheochromocytomas and PGL have genetic etiology. Mutation analysis can guide management of these cancers, particularly for SDH genes, MEN2, VHL, and NF1. First-degree relatives are also screened to determine family history for these genes. Genetic counselors are embedded in endocrinology surgery clinics to help determine plans of action.

These screenings are currently implemented at Penn but have produced inconsistent results at Cleveland Clinic. It does appear to be a useful screen once the kinks are worked out. This screening could be expanded to other tumors and germline syndromes. There is also the opportunity to create best practice guidelines for surveillance, as well as conducting cost-effectiveness studies. ’

Murray Brilliant- Periodontal Microbiome

Murray presented Marshfield Clinic’s project trying to understand the connection between oral and systemic health, particularly between periodontal disease and diabetes. Marshfield has an integrated medical-dental health record that accommodates this. Patients have DNA, plasma, and serum samples in a medical warehouse. Patients often come from rural backgrounds with little access to clinics, so they will capture health records first, then collect periodontal and microbiome data. They will have routine diabetes tests (glucose fast, serum microalbuin, Hba1c screen) and periodontal microbiome samples in addition to a questionnaire. Human Microbiome Project data may also contribute to this. The lowest hanging fruit would make alerts for people who have periodontal disease to be screened for diabetes. EMR data can be aggregated with all of this dental data. Environmental data is included in the questionnaire, and they are now trying to use PhenX to standardize environmental effects.

Geoff Ginsburg- Family History

Geoff presented on the MeTree Family History tool that he developed at Duke. The tool collects a 3-generation family history for 48 diseases with pilot projects in cancers and thrombosis. It generates a pedigree as well as a tabular family history which physicians preferred in tests. Risk stratifications are based on published guidelines, and algorithms have been compiled from multiple sources. MeTree has decision support tools which allow it to be integrated into a clinical workflow. The algorithm updating team is looking at clinical guidelines in clinical areas. Eventually, they hope to have a central data repository with an EMR that can support updating the records. Inclusion of relatives who aren’t consented is currently a research protocol. The team is assessing MeTree for many outcomes, including patient/physician satisfaction, change of health outcomes, patient/physician behavior, and clinical validity and utility. Patient acceptance thus far has been very good, and the provider community has become very supportive. The tool also has >90% sensitivity and specificity. 1000 patients are currently enrolled in MeTree. For the future, Geoff hopes to incorporate additional risk information such as new disease types and new types of risk like genomic testing. He also hopes to add more decision support, create tablet and iPhone apps, and integrate text messaging reminders for patients. Privacy issues also need to be assessed for social networking. Patient controlled records could allow a bypass where patients enter data into something that isn’t an EMR and then messages are sent back to clinicians. A current pilot project uses a patient portal to capture information that is routed to a centralized resource and then reported to the MeTree decision support system.

Howard McLeod- Pharmacogenomics at UNC

Howard presented on UNC’s pharmacogenomics program, which focuses on real endpoints to show the effectiveness of genomic medicine. For CYP2D6, they looked at active metabolite levels after tamoxifen treatment. Intermediate metabolizers had the lowest blood levels, so their dose was altered. Results showed that you could normalize the metabolite levels and proved the effectiveness and simplicity of prospective studies. They focused on patients outside academic centers for more “real world” scenarios. There is now a huge gap in genomic medicine- discovery and validation efforts are plentiful, while practice and policy making efforts are limited. We now need to target clinical administrators, payers, and patients to focus on endpoints like investment returns at medical homes, quality measures,

and patient satisfactions. Preemptive care targeting high-risk populations could eliminate adverse drug reactions and save institutions money. The program developed a list of 61 common actionable variants and found that humans have at least seven on average that can be acted on. The program worked with health administrators globally to develop a national formulary and create a consensus panel for pharmacogenomics markers. The list of variants has very high overlap with CPIC, and most of the variants are on the DMET+ or are common variants. This program is being applied to insurance coverage, identification of variants of low utility, dose selection (for the CYP genes), therapy selection, and preemptive prediction (for HLA-B5701). Patients who move between multiple health system is problematic as certain drug reactions are classified as allergies, resulting in hard stops rather than flags in certain EMRs. Other participants thought that patients need to be engaged and empowered in terms of their own genetic data and health information. Patient portals seem to be the way to navigate this.

Mark Ratain- 1200 Patients Project (Pharmacogenomics)

Mark presented on the 1200 Patients Project, the flagship of the Center of Personalized Therapeutics at the University of Chicago. Patient portals, preemptive genotyping, and individualized virtual pharmacogenomic consults for every patient have improved the efficiency of their system. Tests are done for relevant variants- variants where PGx experts would be willing to tell a physician that their patient has a particular SNP and what it means. They currently are looking for a CLIA lab to run samples, but they expect to return results for PGx consults by February. Patients must be receiving care from a co-investigator and taking 1-6 medications. The study currently has 440 patients enrolled. The physician portal is not linked to the EMR and only provides genotype data, medications, levels of evidence for a drug/gene pair, and a stoplight visualizing risk associated with prescription of the drug. Patients are only told that they would respond better to another drug, but they can choose to accept or ignore this. Potential collaborations would be for a randomized study of preemptive genotyping. All patients would be genotyped, but genotype data would only be given to physicians for half of patients. The number of genotype-associated adverse events would be measured. They are still working on pushing updates into the EMRs. Participants discussed differences in IRB approval for trials where you return results to only part of a study cohort.

Howard Jacob- Medical College of Wisconsin

Howard Jacob presented MCW's approach to genomics, which became famous when they did WGS on a young boy with an unknown disease and found a mutation for X-linked inhibitor of apoptosis protein. MCW only chooses to sequencing if it will affect clinical decision-making and conclude genetic etiology after reasonable amounts of clinical testing have been conducted. The decision must also be cost-effective. Consults are conducted by a medical geneticist and a genetic counselor before consenting sessions with the family. Results are confirmed with downstream biological testing. Families are also allowed to ask for data as part of return of results. There are still many limitations, including unknown utility of WGS and expensive and complicated software. Analysis software is the same that Illumina uses to validate their results, but it is hard to introduce updates into the software. Still, WGS testing is more cost-effective than single gene testing because it can lead to lower-cost prescriptions and provide information on more than the original gene you were targeting. Adding family history data and PharmGKB data would further strengthen the power of WGS. Four out of ten insurance groups have already given pre-approval to pay for WGS as a first-line clinical test. We will need to consider data return and education programs for WGS to succeed. Access to WGS data, EMRs with CDS, validation steps, integration tools, and demonstration projects showing utility, validity, and value will also allow WGS to succeed. Participants thought the group could create best practices for applying WGS and validation steps.

Gail Jarvik- Genome Resources at UW (Cancer)

UW has multiple sequencing programs at their campus. The Northwest Genome Center oversees both the Mendelian Genomic Center and the SeattleSeq exome variant annotation server. The Next Generation Mendelian center focuses on unrelated patients with high locus homogeneity and families (such as trio-based approaches for autism). Validation and replication have been critical for success. UW has also had success as an eMERGE site. There is now CLIA-based sequencing ongoing for breast and colon cancers, and their Coloseq chip can be exported to other sites. They also have the New Exome Technology (NEXT) Medicine project looking at clinical sequencing in colorectal cancer. They will be conducting RCTs using WES to screen for Lynch syndrome and assessing outcomes based on the number of patients with a causative genetic mutation identified. They have also done bioethics research on psychosocial and economic outcomes, as well as other patient and physician experiences. Participants thought WES was beneficial because it avoids alert fatigue since you get all of the results at once.

Scott Weiss – Sequencing

Scott presented on the Partners Center for Personalized Genetic Medicine (PCPGM). PCPGM has a biorepository with 200,000 samples, an EMR, as well as the CLIA-certified Laboratory for Molecular Medicine (LMM), all supported by information technology infrastructure. The LMM performs around 4000 genetic tests a year, focusing on cancer and cardiovascular disease. The center has sequenced for more and more genes per clinical test over time. It will soon cost as much to genotype the whole genome as it will to run the Cardiochip. Analysis capabilities, however, do not compare to the amount of sequencing. WGS will generate 2-5 million variants leading to a wealth of new information. Currently Partners has 2 Hi-Seqs, but they haven't started doing WGS themselves. The amount of work that Illumina, Complete Genomics, and Partners all do is not set, but Partners won't be building a huge sequencing facility. Processes need to allow clinicians to receive and manage genetic results and link them to experts who can better determine the implications of genetic results. The key challenge will be maintaining an evolving knowledge base and updating EMRs. The system has developed GeneInsight, a report-generating engine that can be used as a knowledge base. Heidi Rehm has been working on reporting results from GeneInsight into EMRs. It is currently linkable to EMRs and has been tested at places like Intermountain. Variants of unknown significance are currently classified as pathogenic, which needs to be better refined for the future. The EMRs also need better decision-support tools.

Day 1 Action Items:

- Convene CEOs of health systems around genomic medicine
- Address patient role in light of talks around patientportals
- Certified software for sequence analysis
    - Creating minimum standards of performance
    - Certification with software would be an FDA issue
- Demonstration projects showing clinical utility
- Official codification of the "Milwaukee principles", comparing it to the NIH Undiagnosed Diseases program in how to admit patients and how to choose which patients would best be served by a genomic approach
- Collaborations: creating repositories, trans-NIH IC Sequencing Inventory, SeattleSeq (http://snp.gs. washington. edu/SeattleSeqAnnotation/)

Day 2

Eric Topol- Scripps

Eric presented on the genomic medicine program at Scripps- Idiopathic Disease of Man (IDIOM). It can currently support about 20 patients. They sequence patients with life-threatening illnesses as well as others after committee review. Scripps also runs the Wellderly program to understand the genetics of health aging. Complete Genomics is doing WGS of 1200 patients and WES on 350 of them, with data ready by March. All patients have no illnesses, no medications, and are cognitively intact. Most are of European-American descent Eric suggested that this would be a nice collaboration activity, as this population could serve as a control group for other elderly cohorts or studies on late-onset disease. Scripps also has a pharmacogenomics program where they are systematically genotyping people getting stents for CYP2C19 and considering alternate therapies. They use a POC handheld genotyping system from DNA Electronics which gives accurate genotyping in 10-12 minutes on up to 8 different SNPs. Other drugs being tested include interferon for patients recently diagnosed with hepatitis C and metformin for diabetics. Platform validation has been done at Imperial College. The system works with both saliva and swabs. The POC genotyping system was IRB-approved because it outperformed conventional essays and because data goes into the EMR. The Human Tumor Sequencing (HUTS) program is similar to a program at University of Michigan performing WES and RNASeq on tumor and germline DNA. The biggest issue HUTS faces is reconsenting patients for another biopsy. Scripps also offers a course on genomic medicine.

David Craig - TGen

David presented on the Translational Genomics research team. The Clinical Genomics Center focuses on molecular profiling to expand possibilities for treating cancer patients. Patients with late metastatic disease are sequenced by Illumina and Complete Genomics to identify targets for proper medication prescription. Collaboration could help create a data set for these patients and their outcomes. They have sequenced 50 patients in the last year. Current protocols for WGS involve multiple support layers including CLIA clinical pathology labs, sequencing, and informatics layers in order to validate results. Medium pass WGS and RNASeq are performed alongside exome sequencing to help confirm results. The studies show that tumor-specific variants can be related to treatment. They also look for gene-gene interactions to inform treatment, such as a TP53 mutation associated with amplification in other genes. Multiple high utility events are often found in metastatic diseases. Another ongoing trial involved sequencing of genomes and transcriptomes to determine additional treatment options for triple negative breast cancer. Collaborative opportunities include comparing outcomes and data sharing. Participants discussed running studies to test the utility of such diagnostic programs.

Maren Scheuner- Veteran's Health Administration

Maren presented on the Veteran's Administration (VA), the largest integrated delivery system in the US. Priorities of VA Health Services Genomics Research included building a foundation for research that examines all aspects of translation, developing informatics, developing genomic educational interventions linking practice to patient outcomes, and evaluating implementation models. There are seven genomic centers throughout the country. Their current project examines using family history education to improve genetic risk assessment for cancer. The multi-component education program includes informational, clinical, and behavioral interventions. Tools for red flags were developed, but providers did not find it useful until family history was included and it was more efficient. A survey records patient-submitted information. Health factors generated by cancer family history reminders are tracked monthly. 10% of progress notes are randomly abstracted monthly and assess for changes in

documentation of cancer family history and referrals for genetic consultation. Providers like including cancer family history but don't want to make it mandatory. The providers also requested more education and expert review of health factors generated by system.

Les Biesecker and Bill Gahl, Genomic Medicine Programs at NIH Clinical Center

Bill Gahl presented on the NIH Clinical Center. Anyone who comes in must be on a research protocol, but does not pay anything except a "school tax"; the collaborator pays for the rest. Providers either call up an investigator or apply for a bench to bedside grant. Currently, grants are $135,000/year for 2 years. Right now, the Clinical Center is working on opening up to extramural investigators. NCATS may also change how the Clinical Center operates. Clinical Centers collaborates with the Undiagnosed Diseases Program (UDP) when they find genes with unknown function and they have patients who are incredible well-phenotyped. They have also created software for filtering variants in WES.

Les Biesecker presented on the NIH ClinSeq program which looks at young to middle-aged patients to assess carrier frequency for cardiovascular diseases. He specifically looked at combined malonic and methylmalonic acidemia (CMAMMA), for which they found a potential causative gene and analyzed other patients. They found very increased levels of metabolites when they rephenotyped patients and later found that CMAMMA is caused by mutations in ACSF3. This study first broadly consents patients and gathers omic data. This data is filtered before clinicians make a hypothesis and perform clinical research. They are now comparing WES with positional cloning to avoid Type I error. This cohort could be used at places that want to study unknown variants but are unable to rephenotype.

Participants discussed consents for broader phenotyping. You can bring patients who have already been sequenced and tell them that they have found variants in other people and that they need to see if these variants mean anything. You can also look at sibling and other relatives. They also have tried looking in the 1000 Genomes dataset for homozygotes of these rare variants and could not find anything. They could try SeattleSeq.

Presentation of Pilot Demonstration projects

Cancers (Charis Eng/Gail Jarvik)

1) Lynch syndrome screening

They want to improve implementation of recommendations for IHC/MSI screening for colorectal and endometrial cancer, since 3-5% of all colorectal cancer patients have Lynch syndrome and because it's part of Healthy People 2020 guidelines. They would like to create a resource to evaluate successful implementation of screening. A smaller discovery project would aggregate germline and tumor sequencing with treatment and outcomes including pairs to understand variable penetrance, expressivity, and clinical outcomes. Notably, individuals with identical germline mutations can have different phenotypes and somatic phenotypic outcomes. These cases should go into the pathology workflow with a genetic counselor consult.

2) Neuroendocrine cancer screening

They want to improve implementation of routine genetic screening for medullary thyroid cancer (MTC) and pheochromocytomas/paragangliomas (PGL) since they are already integrated into the American

Thyroid Association guidelines. A resource to evaluate successful implementation of screening can be linked to family history and TCGA projects sequencing rare tumors. TCGA database currently has 4000 exomes, and now there are attempts to look at later stages, response, and treatment options. This would help us determine if we do capture and resequencing or if we do WGS and targeted analysis.

Unused ideas included looking at moderate risk variants and determining clinical utility, very rare phenotypes with no known associated genes, germline and somatic variation associated with tumor progression and drug resistance, and cancers that rarely have somatic alterations.

Periodontal Microbiome (Murray Brilliant)

1) Pharmacogenetics for Dentistry

The first pilot would implement warfarin pharmacogenomic testing prior to dental procedures using a combined EMR and electronic dental record. Warfarin levels often have to go down before certain dental procedures can happen because of excessive bleeding, so timing of warfarin withdrawal could be affected by VKORC1 and CYP2C9 variants, as well as CYP2D6 for pain management.

2) T2D and Periodontal Disease and/or Microbiome Type

This project would identify type 2 diabetes patients and controls with GWAS data and access to dental records. It will see if T2D GWAS signals can be stratified by periodontal disease intensity or oral microbiome characteristics. This is part of a project in oral system health, and we are working with dentists who see the same patients we see in clinics. We are also training dental hygienists to take microbiome samples. This can aid with dental pharmacogenomics in addition to providing a better understand of risks for T2D onset, severity, control genetics, and environment. You can also link this study to coronary artery disease. Participants thought this project could get the attention of administrators because of the reduced number of canceled surgeries this could lead to. UNC has done work with implanting devices for cardiac disease with the same issue. There are also boutique dentistry groups doing pharmacogenomics that have decided to do this for pain control.

Family History (Geoff Ginsburg)

Validating family history information would be an important goal of this project. We would need to confirm the accuracy of patient-entered data and enable updates of information. Possible demonstration projects include developing sets of iterative questions following baseline information and vary their time, as well as creating adaptive patient questionnaires. We could validate information against JHU's Mendelian diseases initiative, OMIM, and information from living individuals. We could also evaluate attitudes, beliefs, and cultural norms relating to providing family information. Small studies could also evaluate the easiest way to gather data and integrate family history tools into a workflow. We could compare stand-alone tools vs EMR-integrated tools, patient-entered data vs patient advocate/nurse practitioner-entered data, or patient-derived data vs. data from clinical settings. Social media and communications tools (Wiki, Facebook, Genealogy) would also be considered. We also need to determine how to use family history information to create education tools with relevant information for physicians. Surveying providers in different settings would aid developing these informatics systems. Family history tools also need to adhere to evidence-based guidelines such as USPTF. Retrospective studies or cluster randomization can determine this as well.

The holy grail project would be to gather and integrate all relevant risk data- environmental, genomic, molecular, and clinical information. We also need to develop methodology for data aggregation. We need access to population studies. The group recommends that structured family history data should be incorporated into all NIH studies that are collecting genotyping/sequencing data and outcomes. They also recommended forming an Advisory Group on Family History to identify opportunities in ongoing studies, advise larger studies on the implementation of family history, and recommend incorporation of family history data into RFAs. Participants thought patient control and patient-centeredness should be a negotiation tool to determine what to discuss at an appointment.

Pharmacogenomics (Howard McLeod)

There was group consensus that PGx testing is ready for practice since we know so much about actionable variants and mechanisms and because there are fewer ELSI issues. Broad preemptive PGx diagnostic testing is preferable to single gene testing with some exceptions (e. g. CYP2C19). We need a coordinated effort to develop best practices for implementation and create a framework for discoveries. Actionability, annotation, and a repository for variants of unknown significance are all necessary. Their proposed collaboration is to compare WGS, VIP capture platform, and low-tech chip-based genotyping platforms to see which methods are better for variant calling and relating drug response phenotypes to genotypes.

Sequencing (Howard Jacob)

The goal of this group was to change the practice of medicine until WGS can be ordered for a patient and used for healthcare, but we need to develop enough data. Needs include standards and best practices, refinement of calling techniques, annotation standards and strategies, and layering of different data. We need to define standards and meaningful clinical reports to keep costs down. Their grand vision is to sequence 100,000 people with EMRs to build a data set of variants, phenotype annotations, and information about incidental findings. Pilot projects include:

1) Make a set of standards, software, and analysis pipeline for clinical use by taking 10 WGS and reference genomes and having interested groups conduct analysis on them
2) Conduct a wet lab bake off to compare sequencing strategies using 10 consented genomes
3) Create a better reference set of genomes and phenotypes using 500 genomes (100/continent) with EMRs, with subsets of extremes of common clinical phenotypes and known rare variants/carriers
4) Establish minimum standards for genomic and clinical phenotyping
5) Work with NIST on developing standard genome types
6) Create central repository of WGS

Participants noted other projects that this project could learn from, including a 100,000 child cohort with GWAS data at Children's Hospital of Philadelphia and the eMERGE cohorts where older populations were better utilized for multiple phenotypes. EMRs from places like Kaiser or HMOs are capturing medications and diagnoses in an efficient way. Other notes included bakeoffs possible squashing any new technology entering the field and figuring out ideal phenotypes and EMR structure. Genetic counselors could be trained in bioinformatics or have partner sites for informatics training.

Miscellanea (Marc Williams)

Marc discussed many things with this group. They thought there should be guidelines/FAQs/best practices made for institutional IRBs, since they seem to be giving different responses to projects. The clinical/research interface also needs to be delineated, especially since genetic testing is done for discovery and then put in EMRs. Clinical characterization of novel variants would also be helpful, as would a research study on merging information from different sources. Proposed projects include:

1) Creating criteria to determine what variants are ready for clinical usage, possibly with the help of a workgroup formed from this meeting and ClinAction
2) Convene meetings between implementation science consultants for putting genomic information into practice
3) Develop a suite of validated methodologies to collect data to answer clinical/research questions
4) Conduct studies on how practitioners feel about genomics

Participants thought defining when you can share EMRs in important, because different states might prevent physicians from knowing genetic results of patients. CPIC is currently deciding what PGx genes are ready for implementation, but they haven't made any difficult decisions for certain controversial genes. Most implementation will probably be local decisions.

Navigating the Boundaries Between Research and Clinical Care

Pearl O'Rourke

Research and clinical care differ in many ways. Research is for accruing data, while clinical care focuses on the individual. Research data is interesting but not ready for primetime, while information that a clinician receives from a lab is truth. IRBs determine if research subjects need consent or a waiver, while clinical care sometimes has consent forms, but not always. "Extreme" researchers don't realize tissue samples come from people, while clinicians, payers, administrations, and IT support rarely have research experience. There are also "straddlers"- researchers, clinicians, IRBs, funders, and IT support who have experience in both. We need a continuous loop between the two realms, and we also need more straddlers who understand both realms. This way, everyone involved in these realms can distinguish clinical utility and validity, properly design IT systems that separate research and clinical data, and understand how payers work. We also need the public to understand why research is important to clinical care. Regulatory issues will also be of major concern. The Common Rule which governs current research was written in the 1970s. The recent ANPRM stating that DNA is identifiable and thus always requires consent will make waivers extremely difficult. Currently, there is very little standardization between current regulations, and there is very little guidance on genetic approaches, resulting in different ruling by IRBs. HIPAA and HITECH policies will also be increasingly important.

David Chambers

We currently see research and clinical care as two separate identities, when really both have the same goal to obtain better information about improving health. Both realms need to be subjected to the same rigor for data collection and quality. We do know that publications and individual training alone won't change practice. The knowledge base in dissemination and implementation is growing at NIH, and there are R01, R03, and R21 grants cosponsored by 14 institutes. 1200 people will also be attending the annual dissemination and implementation meeting, which will be at the North Bethesda Marriott on March 19-20, 2012. Members from this group could attend the meeting to interface with implementation experts. CSR has convened a standing review committee (DIRH) to ensure an expert review of dissemination and implementation research applications, further evidence that these studies

are a bigger part of the research enterprise. We now need to fuse research and clinical care in a more directed way. There is a continual need for large samples and checking broader validity. Many institute-specific efforts are now using their researchers to narrow this gap and integrate more research in clinical practice. The Common Fund's HMO Collaboratory is moving research and practice together in a formalized way.

David Ledbetter

There are at least three types of groups represented here- pharmacogenomics, GWAS/common disease, and medical genetics/Mendelian disease – in the genomic medicine realm. A great deal of genetic testing is already performed in CLIA/CAP-certified clinical labs run by lab directors, medical directors/consultants, and genetic counselors. All of these positions need appropriate national certification, including ABGC for genetic counselors, ABMG or CAP/AMP for laboratory directos and medical directors/consultants. There are already standard procedures and guidelines for moving genetic technologies and testing from research to clinical practice. Professional societies create laboratory guidelines for proper genomic applications in CLIA/CAP certificed labs and also practice guidelines for clinicians ordering new tests. Even though WGS is a powerful new technology, it isn't that different in concept from previous major new technologies. We can apply the pipelines for medical genetics to GWAS and PGx. Nevertheless, medical genetics has done a poor job of assessing clinical value of new technologies and genetic tests.

Dan Roden

These have been really good ways of thinking about boundaries. Working in the EMR blurs the boundary between research and patient care. By deploying WGS into EMR as a tool for clinical care, we start asking research questions which complicate things. We might be taking care of patients at a clinical level who might also be research patients. We need to train more people like clinical geneticists to be in the wards.

Participants supported engaging patients to want genomic approaches to medicine. Wylie Burke's research shows that people want to be asked. We need to be mindful that when you follow regulations, it might not avoid conflicts. We also need to think beyond going to bodies like ACMG to bring trainees and physicians interested in translation into the pipeline. ACGME might already move geneticists too rapidly into specific branches, but there's not a lot of room to fix this if we want to comply with ACGME standards. The Board of Directors of ABMG is contemplating one-year certifications for additional training for oncologists or adult cardiologists. Small centers of innovation within health systems might be the most efficient way to disseminate ideas when ready. In terms of CLIA standards, Heidi Rehm organized the first meeting of CLIA labs at Harvard, and others are talking about guidelines for next gen sequencing.

May meeting planning

Preliminarily, the May meeting will focus on barriers. Standardization of formats might not be practical because of the rapid evolution of platforms. We should discuss barriers with payers, pharmacy benefits experts, CMS, CLIA/CAP certification experts, AMP/ACMG board members, genomics law experts, and even 1000 Genome and genome reference experts. We can also present early deliverables at the May meeting, including "Tiffany standards" (sequencing guidelines) and protocols for evaluating sequencing

platforms. We could also have everyone analyze 10 genomes to begin forming ideas on combining data sets from multiple places

Action Items

1) NHGRI will attempt to help each of the 6 workgroups (Cancers, Periodontal Microbiome, Sequencing, Pharmacogenomics, Family History, and Research/Clinical care interface) to hold some calls between now and May to try and prioritize their pilot projects.
2) NHGRI will invite these groups to meet with the NHGRI Genomic Medicine WG periodically.
3) Each workgroup will present early deliverables at the May meeting.