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Genomic Medicine Centers Meeting III
May 3-4, 2012
Marriott O'Hare, Chicago, IL

Meeting Welcome and Overview – Dan Roden
Dan welcomed the group to the 3rd Genomic Medicine meeting and reminded the group that these meetings were initiated one year ago to begin discussion regarding the implementation of genomic medicine and advise NHGRI on critical areas for further thought and discussion. During the last meeting working groups were formed and multi center genomic medicine projects were presented. The GM3 meeting will focus on the barriers genomic medicine faces in ordinary workflow of healthcare. Stakeholders, particularly those in the reimbursement realm, were purposefully invited and will provide their perspective; each workgroup will have an opportunity to present an update of accomplishments.

Remarks by NHGRI Director – Eric Green
The Human Genome Project will be celebrating its 10th anniversary in 2013. Since this project was completed efforts have been focused on the vision that was published by NHGRI in 2011 describing the path forward in genomic medicine. Success since the end of HGP has been impressive with technologies moving faster than expected. Costs for sequencing along with turnaround time to sequence have dropped. With these significant advances a new strategic vision was created in 2011 outlining 5 domains of genomic medicine for focus: understanding the structure of genomes; the biology of genomes; the biology of disease; advancing the science of medicine; and improving the effectiveness of healthcare. NHGRI is critically focused in the next decade on making the implementation of genomic medicine in the clinical realm a reality. NHGRI will rely on this group and others for advice on how best to make these investments. NHGRI has already enlisted some opinions on this subject and there are varying thoughts as to which speed is appropriate. While some think a brisk pace should be taken others think this should be a sprint. NHGRI wants to explore what the options are for moving forward and looks forward to these meetings with the intention of learning from experts in the field.

Summary of Genomic Medicine 2 meeting in Bethesda – Rex Chisholm & Teri Manolio
Rex outlined several identified barriers to the implementation of genomic medicine:

- Lack of evidence for benefit/value
- Institution and physician acceptance
- Education of patients, physicians, other providers
- Issues related to consent and other ethical, legal, and social issues
- Sample availability and biobanking
- Recruitment for genetic studies

In addition, highlights from the GM2 meeting were discussed. Action items from the GM2 meeting were reviewed and most have been completed or are in process.

Teri shared with the group a funding opportunity through NHGRI for Genomic Medicine Demonstration projects. Proposals for this program should demonstrate feasibility of, and develop methods for, incorporating patients' genomic findings into their clinical care. NHGRI hopes to receive applications from a variety of sites varying in expertise as well as type of sites (health maintenance organizations, community health clinics, private practices, military, VA, underserved and indigent populations). A coordinating center will also be funded.

Additional funding opportunities include Clinical Sequencing Exploratory Research looking for institutions to research the challenges of applying comprehensive genomic sequence data to the care of patients and examine the ethical and psychosocial implications of bringing broad genomic medicine into the clinic. A coordinating center will also be selected.

Summary of Dissemination and Implementation meeting in Bethesda – Marc Williams
A panel comprising key players in this genomic discussion spoke at the Dissemination and Implementation meeting to a group of about 70 individuals. The panel outlined strategies and successes needed to create a better balance with policy and ethics issues. Meeting participants were interested in utilizing social media applications and whether these tools could be used to facilitate research. Another imbalance noted was the lack of MDs in attendance, only two in total. A recommendation has been made to NHGRI to fund a future workshop.

Implementing Genomic Medicine Programs – Laboratories – Heidi Rehm & Debra Leonard
Heidi outlined the Partners Healthcare Personalized Genetic Medicine process and reviewed challenges in clinical implementation. Many of these challenges reflect the rapidly maturing technology and current need for validation for WES/WGS. One approach to overcome these challenges includes supplementing each of these tests with an additional platform for validation or analyzing the exome/genome with multiple technologies. This is a time consuming process. Another issue that was addressed was the lack of available clinically annotated variants. ClinVar is a public database being created to catalogue a large number of variants. Another substantial concern is that of updating medical records with new information on a given variant. GeneInsight paired with an EMR can facilitate this process and serve as a hub between the research lab and the clinic. It is important for labs to collaborate before and after entry to the clinical realm. Payers should encourage this participation.

Debra presented the pathology perspective on clinical genomics. A framework straddling the divide between discovery and test validation/clinical utility was outlined utilizing CAP and CLIA standards. In addition, understanding of the human genome combined with sequencing technology advances is moving this field toward genomic medicine. Genetics, oncology and infectious diseases show the highest growth in clinical care. Growth in genetics can be attributed to the ever decreasing sequencing costs. Recent advances in technology are driving the adoption of genomic analysis in pathology labs. NextGen sequencing is the next tool pathology labs are considering with the understanding that this new technology will not replace every test. There are currently no CLIA/CAP or FDA guidelines for NextGen sequencing. All pathologists can play a key role in genomic medicine and should be present for these discussions.

Implementing Genomic Medicine Programs – Laboratories – Hawazin Faruki
After a brief introduction of LabCorp, Hawazin outlined three bins that make up their diagnostic program: science, regulatory and commercial. She also shared statistics concerning the number of opportunities reviewed and new tests introduced each year. LabCorp criteria for selecting an opportunity are analytical & clinical utility, actionable result, reproducible study conclusions and publications, guidelines, and professional society endorsements. Other considerations include: reimbursement outlook, overall cost, IP, feasibility, regulations, and market dynamics. Some examples were given of successful and unsuccessful opportunities. Payer reimbursement is also a key factor. CPT codes will be changing in 2013 and may provide greater transparency, however specific coding for whole genome sequencing has not yet been proposed. It has been difficult to obtain a new CPT code, a hindrance since reimbursement is dependent on these codes.

Sequencing Workgroup – Howard Jacob

This workgroup is focused on returning results from genome and exome sequencing for patient care. There are five main areas of focus: central repository for clinical comparisons, analytical best practices, standards for reporting genomic data, regulatory oversight and consenting, and lab best practices. The group has outlined substantial work plans. The group plans further evaluations to ensure that they are not duplicating efforts and also to complete the tasks that they do engage. The workgroup was encouraged to prioritize key items. Many participants agreed that outlining guidelines would be beneficial.

Implementing Genomic Medicine Programs – Standards – Sean Tunis & Ned Calonge
Sean believes there is a need for refined research questions, developed study protocols and clinical trials. Gaps in evidence need to be reduced to better engage decision makers such as patients, clinicians and payers. FDA, Medicare and BCBS guidelines for clinical utility were outlined. The main focus was on accuracy and that benefits outweigh the risks. Evidence should correlate to a disease, injury, illness or condition. SACGHS has encouraged HHS to create a public/private entity for stakeholders to develop an effectiveness guidance document that will provide reasonable confidence of improved healthcare outcomes for genomic medicine. A meeting is scheduled for later this month with stakeholders to define what kind of evidence would be necessary to define clinical utility and to acknowledge that stakeholders be included in creating these tests.

Ned noted that over 200 foundations are now funding projects to improve healthcare. However, there are no genetics projects. EGAPP's goals and approaches were outlined as well as its process for creating a recommendation. An analytic framework was discussed but there are gaps in every step of the process concerning analytic validity, clinical validity and clinical utility. Goals include reducing the noise levels and utilizing modeling to fill the gaps, providing clear recommendations for actionable results, developing study designs and collaborating across networks. The idea of utilizing tiers and bins could aid in defining a clear link between research and clinical use. These bins should be developed based on evidence and type of application.

Implementing Genomic Medicine Programs – Financial Impact – Naomi Aronson, Joanne Armstrong, Reed Tuckson
Naomi presented a brief overview on the BCBS Network and their Technology Evaluation Center (TEC). Genomics is in some ways much like radiology and imaging were years ago, and genomic medicine can learn from this. Payer support of any new testing or technology is contingent on affordability and on direct benefits to patients. Cost effectiveness is especially important as healthcare costs continue to rise. By utilizing comparative effectiveness strategies to manage a condition, real-world practices and variations in patient populations can be addressed and outcomes improved. Another area discussed was Patient-Centered Outcomes Research – granting patients a voice in assessing their health care options and in making informed decisions.

Joanne noted that spending has been rapidly increasing along with concerns regarding poor quality and misallocation of resources. Genetic testing is on the rise and expected to grow 20-50% in the next year. A key question is whether genetic medicine will improve the quality of healthcare or drive additional medical costs with marginal healthcare gains. Challenges that genomic medicine will have to overcome with the payers are concerns about effectiveness, effective decision support tools, CPT coding challenges, privacy considerations and disparities in use of genetic technologies. Marketing to consumers and physicians has also resulted in increased payment. Requests from patients and physicians drive the demand and can result in medically inappropriate and non-evidence based requests for testing. Other concerns from Aetna include the shortage of trained genetic specialists, substantial knowledge gaps in the clinical workforce and a lack of genetic literacy by consumers. Disease-specific genomic services were suggested as strategies to promote evidence based use of genomic medicine. Other strategies included online resources and member

guides. Genetic counselors were also encouraged and should be reachable via phone as needed. Privacy is also clearly a key factor with genomic medicine.

Reed of UnitedHealth Group noted the rising cost in healthcare and how, unlike most other industries, many new innovations bring a higher cost. Higher costs must be met and result in higher costs for the consumer. Because of this cost pressure, innovation for the sake of innovation can result in real harms such as churn in the system, added time for interpretation/education/ decision making, and unclear processes or guidelines for action, particularly for incidental findings. The innovation that payers are looking for is innovation that improves the quality of healthcare and also reduces the overall healthcare cost, like innovations that get to the root cause of a disease. He encouraged the group to reach out and collaborate with Sean Tunis and groups like his to create a gold standard for implementation. He also suggested a realignment to focus on primary care patients in an effort to solve the soaring costs of medical care. Stakeholders need the genomic medicine community to succeed since they have the tools to solve problems that most disciplines cannot.

The group discussed the costs related to genomic testing, both initial and downstream and how these costs would be covered. Some advocated whole genome genotyping to bring down the costs of genotyping; payers and lab stakeholders countered that this raised other issues of what to do with all of the additional information – how it would be maintained, curated, communicated, and updated, etc. It was suggested that the payers fund research studies in an effort to work through strategic implementation plans and overall costs. With this type of collaboration, some hoped that payers would be able to share whatever data they have available. Those with expertise in the clinical laboratory stated that even though the cost of the test has not dropped, the content has increased and continues to do so which was encouraging to the payers. Tying genomic testing into the care pathway of a patient is critical. The payers emphasized that cost by itself was not an issue as they would be willing to pay for and support good, actionable tests.

Implementing Genomic Medicine Programs – Public Health – Toby Citrin
The core functions of public health in regard to genomic programs include assessment, policy development, and assurance. These three areas are also relevant to medical care interface. The public health sector continues its relationship with GAPPNet in an attempt to support streamlining genetic research to obtain an evidence base. Stakeholders are being consulted from the public health sector in an effort to get opinions on the leading priorities to advance genomics in the next 5 years. Public health workers understand the potential of genomics to reduce morbidity and mortality. Current efforts include newborn screening with the potential for programs to implement a genomic component. Expectations of medical care are broken into four categories: practice, education, policy, and partnership, each of which is important when considering genomic medicine. Collaboration is the way to speed up the translation pipeline. Policies need to be implemented to bring genomic medicine into the EMR with decision support tools. The public health sector also needs support in utilizing these genomic medicine tools. Health disparities are a large focus of the public sector but the promise of genetic research is twofold - the cost could only allow the "haves" to take full advantage or it can be used to help address diseases that are creating health disparities. A variety of partnerships are being formed in different sectors of healthcare with the public health sector hoping to advocate for patients and healthcare at large.

Family History Working Group – Geoff Ginsburg
This workgroup was formed in December of 2011 to create a research agenda and use principles of science to put family history into the workflow. The group has reviewed two different web-based family history tools: MeTree at Duke and Our Family Health at InterMountain. This group will work with Epic to evaluate the ability to integrate family history software and decision support tools into

the EMR. It will also investigate the potential of social media tools to capture family history data for transmission to providers. The Family History workgroup will also work to gain knowledge and implement family health history intervention and outcomes. It was suggested that this workgroup contact Northwestern or Mount Sinai (eMERGE sites) who have been in contact with Epic concerning modification of Epic tools. Erwin Bottinger supported the idea of custom tools but warned that too many changes may result in a system that does not work across sites/networks.

Periodontal Microbiome Working Group – Murray Brilliant
The goal of this group is to establish an oral/systemic health research network by sharing patients and data across networks to advance translational medicine and dental care. The hope is to accomplish this through institution of standards and best practices. Many sites are already collecting this data or have plans to begin collecting this data. These sites will be looking at microbiomes on a research basis. These microbiomes would need to be sequenced in order to place them into a clinical setting. There is a great deal of interest among the microbiology community in sequencing microbiomes. The group is in the beginning stages of this work but has well defined inclusion/exclusion criteria, definitions, and protocols. The group will also continue efforts to form a national network of institutions to establish a large and diverse cohort of dental/medical patients with EHRs, EDRs and oral microbiome samples.

Implementing Biomarker Programs – Paul Ridker
Paul walked the group through trials he had conducted showing some of the methods used and results that were obtained. Practice guidelines are important for the payers but they are not always evidence based. Four crucial questions for moving a biomarker from the bench to the clinic were outlined, all based on evidence. It is unclear whether screening will play a role in clinical care and if PGx will have an impact. Paul spoke to Eric Green's density maps on the speed of translation to practice, noting that it takes a long time to change clinical practice. Randomized trials help move genomic medicine into clinical care as do apps, and we have to remember that all of this does matter to patients.

Clinical/Research Interface Working Group – Pearl O'Rourke
This group will focus on exploring the boundaries between research and clinical practice and their relevance. Pearl noted the importance of bi-directional flow of data between the research lab and the clinic and the tension associated with this flow. There are many gaps to address including how to get genetic information into the EMR. The gap between researchers and physicians will need to be better defined so there can be better collaboration. The patient's role is also critical and should be consideration since it is ever changing along with their expectations.

Pharmacogenomics Working Group- Howard McLeod
The workgroup's charge is to identify one or more collaborative demonstration projects that would advance implementation of pharmacogenomics into clinical practice. One key question is whether NextGen sequencing is valuable for implementation of PGx. The group will look to the eMERGE Network, which is applying the PGRN-derived custom approach Network-wide, to better define outcomes and measures. Other items for the group include a meta-meta-analysis, comparison of the advantages/disadvantages of current platforms for PGx, and the idea of who will push the PGx agenda forward.

Implementing Physician Education Programs – Eugene Passamani
Genomics can contribute positively to clinical care, and there are many opportunities for use in a clinical setting. Clinicians have a genuine interest in and apprehension towards genomics; however there are some successful and informative lecture series available. Problematic areas include

varying degrees of knowledge, needs/wants, and areas of specialty. Education through professional associations is nuanced, since they worry about getting ahead of their membership and wasting funds but they also do not want to be behind. To effectively educate physicians the traditional route cannot be taken. Starting with PGx may be a good first step since most physicians prescribe medications. It would be useful to engage with physician societies to implement education tools and programs.

High Priority Areas for Evidence Generation and Prelude to GM4 Meeting
The day was reviewed with brief descriptions of the presentations from Day 2 followed by ideas for next steps. The group should take the challenge presented by the payers to identify evidence for outcomes. It was also proposed that to keep the momentum of the group strong, the GM4 meeting could potentially be moved to September and include a focus on standards for sequencing, reporting, and documenting in the EMR – this may also become a subgroup. Stakeholders should be the theme of GM4 with potential guests to include professional organizations, research organizations, patient groups, EMR vendors, regulatory groups, public health departments, and other private genome efforts.

Action Items:

1. Continue engagement with payers to further discuss a plan to identify evidence for outcomes.
2. Work to invite physician societies and groups to the next GM meeting to discuss future collaborations.

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Attending

Aetna	Joanne Armstrong
Air Force	Ron Miller
Air Force	Cecili Sessions
U. of Alabama	Jonas Almeida
Baylor	Wojciech Wiszniewski
BC/BS Association	Naomi Aronson
Brigham	Paul Ridker
Brigham	Scott Weiss
U. of Cal., San Diego	Kelly Frazer
U. of Cal., San Diego	Oliver Harismendy
Ctr for Med Tch Policy	Sean Tunis
U. of Chicago	Yusuke Nakamura
U. of Chicago	Peter O'Donnell
U. of Chicago	Mark Ratain
Cincinnati Children's	Beth Cobb
Cincinnati Children's	John Harley
Cleveland Clinic	Charis Eng
DCCP/NCI	Andrew Freeman
Duke University	Geoff Ginsburg
U. of Florida	Julie Johnson
Geisinger	Andy Faucett
Geisinger	David Ledbetter
Geisinger	Marc Williams
Intermountain	Steven Bleyl
Johns Hopkins	Chris Bradburne
Johns Hopkins	David Valle
LabCorp	Hawazin Faruki
Marshfield Clinic	Murray Brilliant
Marshfield Clinic	Laura Nelson
U. of Maryland	Scott Devine
Med. College of WI	David Dimmock
Med. College of WI	Howard Jacob
U. of Michigan	Toby Citrin
Morehouse	Adam Davis
Mount Sinai	Erwin Bottinger
NHGRI	Maggie Bartlett
NHGRI	Ebony Bookman
NHGRI	Alvaro Encinas
NHGRI	Eric Green
NHGRI	Mark Guyer
NHGRI	Lucia Hindorff
NHGRI	Rongling Li
NHGRI	Teri Manolio
NHGRI	Bradley Ozenberger
NHGRI	Eugene Passamani
NHGRI	Laura Lyman Rodriguez
NHGRI	Jeffrey Schloss
NHGRI	Jeff Struewing
NHGRI	Simona Volpi
NHLBI	Dina Paltoo
NIMH	Patrick Bender
U. of NC, Chapel Hill	Federico Innocenti
U. of NC	Howard McLeod

Northwestern	Rex Chisholm	Thomas Jefferson U	Scott Waldman
Northwestern	Peter Kopp		
Northwestern	Maureen Smith	UnitedHealth Group	Reed Tuckson
OIVD/FDA	Zivana Tezak	US Dept. of VA	Ronald Przygodzki
Partners Healthcare	Michael Murray	VA Great Los Angeles	Maren Scheuner
Partners Healthcare	Pearl O'Rourke		
Partners Healthcare	Heidi Rehm	Vanderbilt U. Med Ctr	Melissa Basford
		Vanderbilt U. Med Ctr	Josh Denny
U. of Pennsylvania	Katherine Nathanson	Vanderbilt U. Med Ctr	Dan Roden
Saint Jude	Mary Relling	U. of Washington	Debbie Nickerson
The Colorado Trust	Ned Calonge	Washington University	Rick Wilson
Ohio State University	Murugu Manickam	Weill Cornell	Debra Leonard