Rapporteur: Ian Marpuri
Program Analyst, NHGRI

Genomic Medicine Institutes' Colloquium
June 29th at 10:00 AM CDT
Marriott O'Hare, Chicago, IL

Participants: David Bick (Medical College of Wisconsin), Erwin Bottinger (Mt. Sinai), Murray Brilliant (Marshfield Clinic), Rex Chisholm (Northwestern), Richard Cooper (Loyola), Charis Eng (Cleveland Clinic), Greg Feero (NHGRI), Elise Feingold (NHGRI), Kelly Frazer (UCSD), Andy Freedman (NCI), Gary Gibbons (Morehouse School of Medicine), Geoff Ginsburg (Duke), Eric Green (NHGRI), Bruce Korf (UAB), David Ledbetter (Geisinger), Thomas Lehner (NIMH), Jim Lupski (Baylor), Teri Manolio (NHGRI), Ian Marpuri (NHGRI), Clay Marsh (Ohio State University Medical College), David Mrazek (Mayo Clinic), Michael Murphy (Partners Healthcare), Peter O'Donnell (University of Chicago), Brad Ozenberger (NHGRI), Dina Paltoo (NHLBI), Jon Pollock (NIDA), Dan Rader (University of Pennsylvania), Mary Relling (St. Jude's), Dan Roden (Vanderbilt), Laura Rodriguez (NHGRI), Jeff Schloss (NHGRI), Alan Shuldiner (University of Maryland), Jeff Struewing (NHGRI), Danilo Tagle (NINDS), David Valle (Broad Institute), Dick Weinshilboum (Mayo Clinic), Marc Williams (Intermountain Healthcare), Rick Wilson (Washington University in St. Louis)

Introductions and Objectives *Geoff Ginsburg and Teri Manolio*

Geoff stressed that much of this meeting's relevance stemmed from the recent NHGRI Strategic Plan. Geoff and Teri urged participants to consider the implementation and science components to move genomics into the clinic, as well as what specific research and infrastructure needs should be prioritized so NHGRI can integrate them into its implementation plans. Possible outcomes include writing groups to produce perspectives papers or best practices guidelines for implementing genomic medicine, planning groups for workshops or conferences to refine genomic medicine, or even the creation of a network or consortium for collaborative studies.

Role of genomic medicine at NHGRI *Eric Green*

Eric summarized the role of NHGRI and its 2011 strategic plan in relation to genomic medicine. He noted the plan is written for consideration by the entire research community, including multiple NIH Institutes other than NHGRI, which is why so many have sent representatives to the meeting. The strategic plan provides a broad vision without specific implementation projects, so NHGRI is now focusing on developing such projects. The current plan is much more clinically oriented than previous strategic plans. He briefly described the three current implementation working groups, in Basic Science, Disease-Agnostic (general or infrastructure projects), and Disease-Oriented (disease-specific projects in partnership with other Institutes that could be paradigm-setting). He emphasized the need to develop priorities and work with other institutes to obtain needed expertise and address budget issues.

Ongoing and Planned Implementation Projects *Chairs: Jim Lupski and Michael Murray*

CYP2C19 and antiplatelet rx *Alan Shuldiner, Erwin Bottinger , Clay Marsh, Dan Roden, and Dick Weinshilboum*

Alan discussed initial research in the PAPI (Amish Pharmacogenomics of Antiplatelet Intervention) study showing that patients had widely varying platelet aggregation responses to clopidogrel, with 12-33% of patients resistant to it. The trait has an estimated 70% heritability and GWA studies have identified CYP2C19*2 as a loss of function variant underlying much of the resistance. This eventually led to the FDA changing the Plavix package insert to include risks associated with the CYP2C19 variant. Barriers to routine testing for CYP2C19 include lack of randomized control trials, CLIA issues, reimbursement,

logistics, and need for health provider education. Despite this, patients seem to appreciate the value of testing, possibly by viewing advertisements, and come in requesting it or even with genotypes in hand. University of Maryland is now instituting the PAPI-2 study as a prospective randomized trial for genotype-directed therapy in determining whether patients should get clopidogrel or an alternative drug prasugrel. The PGRN Clinical Pharmacogenetics Implementation Consortium (CPIC) has worked to assign likely CYP2C19 phenotypes based on genotype and develop treatment guidelines. Subsequently, the PGRN Translational Pharmacogenetics Project (TPP) is working to translate these CPIC guidelines in patients requiring anti-platelet therapy, develop decision support software for EMRs, and design implementation strategies and metrics. This project has been adopted by Mt. Sinai, Ohio State, and Vanderbilt. Current barriers include dealing with other indications such as stroke or peripheral artery disease, discerning the role of other genetic variants, obtaining rapid and standardized platelet function testing, and administering higher doses of clopidogrel to those with poorer metabolism. Turnaround time is problematic; if there's really a time crunch it may be best to put the genotyping in the chart before it's needed, in a pre-emptive way, as Vanderbilt is doing. Participants discussed the usage of the term "guideline" by CPIC because of its impact on professional societies and recognition by consumers. Genotyping efficiency must also be improved, as it takes considerable effort to implement each of these genotype tests but at some point many will be needed simultaneously. Cardiologists are demanding point of care testing and UMD has established a CLIA environment for genetic testing in the hospital itself. Interactions with EMR vendors and meaningful use criteria will help facilitate adoption. The CDS software in place for over a decade is not suitable for genomic applications; modifications will be needed.

Risk/susceptibility testing (Lynch syndrome, BRCA1/2, etc) *Charis Eng and Marc Williams*

Charis discussed using genomics to identify persons with or at risk for HPNCC (Lynch syndrome) and breast cancer. Around 3% of cases of colorectal cancer in studies in Ohio and Finland had with mutations in mismatch repair (MMR) genes. Microsatellite instability (MSI) analysis and immunohistochemistry are performed on all colorectal cancer patients to determine whether to use 5FU chemotherapy, as 5FU in IHC null gives no survival advantage. Cleveland Clinic currently offers genetic counseling to all screened patients with 80% uptake, and patients who are MSI+/IHC null meet with a genetic counselor for evaluation. The other regional hospitals in the health system have their own pathology labs and do not do IHC/MSI testing, but soon centralization of clinical pathology services will rectify this. Although there is potential value in mutation screening for endometrial cancer, local gynecological pathologists don't have the same interest; a clinical champion is critical to initiating an implementation program. Another barrier is the multiple players doing pathology for individual cases. Cleveland Clinic is also testing the MyFamilyHealthHistory tool to make pedigrees for breast cancer. Genetic counselors will be vital to this.

Marc added that many clinicians cut themselves out of the loop voluntarily because they thought they were going to mess up the process, miss the follow-up, etc. In his experience, engaging them to order testing should be a last resort and doing it any other way is preferable. Programs that cut them out of the process with their agreement have worked well.

Participants discussed workflow issues in getting test results back to clinicians. In these studies, there was often a need for a non-clinician at a choke point for test result return (often an oncology genetic counselor or nurse) to take ownership of cases and ensure follow ups and confirmatory testing. Communication back to the clinician that a given patient has Lynch syndrome is also necessary. The biggest barrier discussed was 3rd party reimbursement for confirmatory testing. Estimated costs per screened case are ~$400, per detected case ~$16K.

Family history implementation (breast, ovarian, colon CA) *Geoff Ginsburg*

Geoff discussed the translational pathway and how to integrate findings into practice quickly. Duke uses a genomic testing advisory committee to identify tests that are ready to use. The rapid learning laboratory approach involves identifying primary care and specialty practices that want to use genetic testing and allowing them to implement certain concepts and tools more quickly than in a clinical trial, allowing for rapid innovation and novel testing. Effectively using family histories became a primary target for the learning laboratory. The Guilford County Family History Project is a collaboration among primary health care, community health, and academic facilities to improve screening decisions, patient outcomes, and provider metrics. It was designed to optimize data flow so that family history data could be entered by the patient into MeTree software and be available for physician usage at the patient's first appointment. The software already has risk-calculating algorithms, well-documented risk stratifications, and can create a pedigree in chart or diagram form. It also creates a physician report with recommended actions, indications, and points to consider, as well as a simpler patient report with the same information. The algorithm is routinely updated, and the model created is both scalable and transferable, as well as valuable in understanding outcomes on a patient, physician, and systems level. It also establishes an implementation sciences framework. Participants discussed the reliability of patients' accounts of family histories and the challenges of including adoptees, orphans, or those with small nuclear families and uninformative family histories.

Complex disease risk advice (MI, T2DM) *Erwin Bottinger, Rex Chisholm, Geoff Ginsburg, Clay Marsh, Dan Rader*

Erwin emphasized the differences in pharmacogenomics and common disease risk genetics. Pharmacogenomics is more on an individual level and focuses on choosing proper drug therapies and predicting adverse events acutely, while common disease risk genetics acts more on population and behavioral levels and may have lifetime implications. Many SNPs have been identified through genome-wide association studies, but individually they have a small impact. Multi-gene risk scores can improve models like the Framingham risk scores to better classify intermediate risk groups to determine more definite treatment pathways. This approach could carry over to conditions such as macular degeneration and non-diabetic kidney disease in persons of African ancestry. Genetic risk may be perceived differently than traditional risk factors and may increase provider usage of treatments and drive patients more actively to change risky behaviors. Risk alleles also need to be considered in the context of minority populations because of differing allele frequencies, since many foundational GWA studies were conducted in European populations and then extrapolated to all populations. Patients have shown a high level of interest, particularly in heart disease, cancer, and diabetes, and interest doesn't differ by ethnic group. Integration of research into this clinical workflow is critical. Mt. Sinai's Institute for Personalized Medicine (IPM) reconsented patients from its Biobank for a prospective randomized trial for primary prevention of CAD. IPM worked with EPIC to integrate Biobank info, and in the future patient-entered data will also be used. Projects are typically funded with internal institutional resources and sustainability is questionable. Participants discussed how to implement genetic testing in places where the population may not be literate in genetics. Genetic counselors remain the best model for delivering this information but we're running out of counselors. Erwin mentioned an advisory group of community members who helped shape the study. Other sites discussed screening for monogenic diseases that in many ways seem to act like polygenic diseases (sickle cell or cystic fibrosis modifiers, for instance), as well as chronic diseases.

Tissue-based genotype-driven treatment *Kelly Frazer, Dan Roden*

Kelly listed 12 targeted gene therapies that are FDA approved and available at present and noted that number is likely to increase rapidly. UCSD is focusing on identifying mutations in gliomas, pancreatic, and breast cancer to allow for novel drug testing. Patients are consented for genomic studies and entry into clinical trials for repurposing of approved drugs. UCSD now performs ultra-deep sequencing (24,000X) to look for mutations in minor cell populations within tumors since they are usually heterogeneous. RNA Seq studies are also being conducted at UCSD for targeted therapies where expression profiles are important, such as MCL1/Myc interactions. Vanderbilt is currently performing molecular profiling in melanoma and lung cancer and compiles this mutation information in MyCancerGenome software.

Other genotype driven treatment decisions *Mary Relling, Murray Brilliant, Rex Chisholm, Geoff Ginsburg, David Ledbetter, Dan Roden, Alan Shuldiner, Dick Weinshilboum*

Mary presented St. Jude's preemptive genotyping approach for all patients, which integrates both a Cerner EMR and pharmacogenetics (starting with CYP2D6 and TPMT). Alerts in the EMR only fire when a high-risk drug is about to be used in a person with a high-risk diplotype. They use the Affymetrix DMET array (with add-on copy number assay for CYP2D6) for wider coverage rather than focusing on 1 or 2 genes, and additionally the array is CLIA-approved in at least one lab. CPIC surveyed experts to prioritize gene/pairs to be reviewed and makes recommendations as to which gene/drug pairs are most useful. They have now created the PG4KDS protocol to migrate PGx into routine patient care determine how often patients have actionable results. Results, particularly for 2 genes (TPMT and CYP2D6), are provided in a special pharmacogenomics tab in EMR. High-risk diplotypes are listed in the patient's problem list in the EMR. They also do pre-test alerts when a high-risk drug is ordered without risk testing. Diplotypes are matched with phenotypes and then linked to EMR priority status. Resolving the genotyping can be challenging; 8% of patients have unresolvable diplotypes for TPMT and all new 2D6 diplotypes require manual review. Phenotypes are translated to an EMR status (priority, routine, further review) and program "DMET tracker" written to incorporate data into EMR. Mary estimates that up to 20% of patients will require pharmacist consults given the prevalence of high-risk diplotypes using just 2 genes.Issues have arisen with finding enough personnel to interpret findings and finding real clinical labs to do arrays. Participants discussed issues with payers not funding DMET testing because it is preemptive. David Ledbetter suggested that more researchers need to approach the payers (particularly nonprofits) to engage them. Participants also noted that in most cases, special individuals have the genetics expertise of many people which reduces costs, but in newer labs you cannot guarantee this and thus funding manpower is important. Funds are needed not just to run the arrays but to interpret the findings. NHGRI can play an important role in improving the quality of the arrays.

Sequencing for unknown disease diagnosis *David Bick, Jim Lupski, Michael Murray, Rick Wilson*
David described the use of whole genome sequencing to help diagnose unknown diseases, often in patients who've undergone lengthy diagnostic odysseys. Samples are sent to Illumina's CAP-certified lab (required by hospital by-laws) and WGS is done on Hi-Seq, producing a variant table which is returned to the hospital. Cases are nominated by two doctors in a particular specialty and presented before a selection committee made of ethicists, geneticists, clinicians, genetic counselors, and chaired by the Chief Medical Officer of Childrens Hospital of Wisconsin. This program is purely clinical. Families can choose what types of information they are told, particularly regarding incidental findings. The Advanced

Genomics Laboratory (AGEN) which is part of the CAP-certified Department of Pathology and Laboratory Medicine, Children's Hospital of Wisconsin receives the variant table and reviews it with Carpe Novo, a validated custom-designed software program and a list of possible genes from the doctor and geneticist. Abnormal results are confirmed by Sanger sequencing. Establishing the clinical/laboratory workflow took six months, and the consent process for each patient can take 6-8 hours. Common formats for these variant tables are badly needed across sequence platforms and could be developed and instituted by NHGRI. The Institute could also contribute in helping evaluate the dominant error modes of NGS and in finding ways to reduce the consent time. Methods to assess whether missense mutations are clinically relevant through proteomics, model organisms or other faster methods could be developed by the Institute. Michael presented a similar system at Partners Healthcare for cases with increased likelihood of being autosomal recessive and improving management. Custom GeneInsight Clinic Interface is FDA registered as a medical device. Frequent software updates are needed to identify gene variants being reclassified as high-risk because of additional research; these then require specialized follow-up.

Overview of genomic medicine efforts related to cancer *Rick Wilson*
Rick presented work on somatic cytogenetic analysis that has been used to stratify risk, particularly for acute myeloid leukemia. This has been used to create disease progression models, as well as determining whether to use treatments like ATRA. Genome-guided medicine has identified multiple mutations, particularly in DDR2 and ESC1 that could be actionable. Participants discussed that finding rarer submutations in addition to prevalent mutations could help tell this story better.

Overview of implementation science *Marc Williams*
Marc presented ways that we can improve uptake of treatments, as evidence of benefit is usually presented to a patient but that does not guarantee they will use it. Culture and system resistance are sources of inefficiencies. In order to implement evidence-based treatment, it must be properly disseminated. Part of this relies on proper process management, having the right data available in the right hands for the right person at the right time and place. Consequences of this can be measured as physical (medical), service (satisfaction, access), and cost outcomes. For a study on Lynch syndrome screening, proper workflow was observed with an automated tracking system. Care providers didn't want to be part of this system, so other personnel were involved. Participants discussed if cutting out the doctors would be bad, but Marc described Intermountain's "pods of knowledge centers" for each department that are tasked to know what is in the literature and each part of the workflow to assist doctors.

<u>Necessary elements for implementation: overview and specific case example for each topic</u>

Methods for generating evidence of clinical utility *David Mrazek and Dick Weinshilboum)*

- **Study designs: registries, trials, etc**
- **Tailoring evidence bar to potential risks involved**

David discussed implementing psychiatric pharmacogenomic testing at Mayo Clinic. There were 6 main barriers to this: 1) determination of evidence needed to initiate adoption 2) educating physicians 3) creation of physician decision support algorithms 4) integration of interpretive reports in EMR 5) development of consensus based guidelines 6) cost and reimbursement. The first issue may be solved by pragmatic clinical trials in real world settings rather than RCTs. Reporting of recommended medications in context of a patient's pharmacogenomic profile was done with a green/yellow/red coding system to show which medications were ok and which needed caution. Initial data suggest

substantial reduction in depressive symptoms with pharmacogenomic-directed treatment, and anecdotal evidence suggests some patients benefit markedly.

Policy agenda for implementation *Dan Roden*

Dan defined the policy agenda as addressing institutional barriers (consent, funding, infrastructure), external barriers (CLIA, FDA, reimbursement), and taking an implementation project from A-Z. He noted that 65% of Vanderbilt patients are exposed to at least one drug with a PGx important variant, and 15% get four. He described the PREDICT project, a study on patients at high risk of receiving an actionable PGx drug where they are genotyped and proper tools put in place for proper point of care treatment. Factors that need to be focused on are figuring out what drugs this study needs to cover, determining the most valid genetic markers, and creating proper POC decision support. Decision support is particularly important when these studies want to scale up to many SNPs and variants, which all need to be communicated in an orderly way, so EMR development is vital. Involvement and commitment from the institutional leadership is critical as well. Clay suggested that first implementing these studies in target populations rather than a general basis would be more effective.

Useful models of research networks for clinical implementation *Murray Brilliant*

Murray spoke about the usefulness of research networks, such as eMERGE, PGRN-PGPop, HMORN, and CTSAs to cross-validate electronic phenotyping algorithms, increase power for analyses, and find the best practices in these networks. Many of the network EMRs don't have standardized responses or have little description of data entry, so harnessing these would increase their utility. Incorporating microbiome data may also be of value. eMERGE has a huge biorepository for studying EMRs in genome science, but diversification of its membership would make it more useful to other institutions. Participants worried about how institutions outside of current networks could become involved, and how data sharing would work in those instances. In general, there need to be lots of agreements about compiling data sets, doing proper data cleaning and quality control, as well as using standard formats and vocabulary.

Identifying potentially actionable variants *Rex Chisholm*

Rex noted that making variants actionable requires they first be discovered; NHGRI should take the lead in encouraging and funding research to make associations between genetic variation and disease. Observational studies may supplant RCTs because there are enough time and resources to do RCTs for every variant. He cited a paper by Berg, Khoury, and Evans in determining WGS approaches and characterizing their actionability as having utility, validity, or unknown. There also needs to be a feedback loop in compiling sequences and validating them. They then need to be placed in one centralized data source for genetic variation with evidence for clinical relevance. This repository should continuously update EMRs, and the repository itself should be curated. NHGRI should make an effort to capture every human genome that's sequenced and as much phenotypic information as one can gather. Participants discussed tracking down patients when penetrant alleles are found and consent prevents you from looking for them. IRBs and physicians should be surveyed for their views on these issues. Another issue discussed was helping clinicians make decisions, as some variants may only be actionable for certain purposes. This was seen as a place where networks could create a consensus for evidence and guidelines.

Developing educational toolbox for healthcare providers *David Ledbetter*

David discussed coming up with innovative educational tools to compliment conventional tools like CME programs for physicians and healthcare providers, the medical school curriculum, and educational tools and websites. He noted that traditional educational models haven't worked for the Surgeon General's Family History Tool. David Bick has videos on YouTube for WGS education that are outstanding. EMRs also serve as educational tools for clinical support. The public has been exposed to sites like 23andMe, Navigenics, deCodeMe, and ancestry.com, which show that there is a general appreciation for genetics. Educational tools also often fail to have formal analysis. A push may need to be made for alternative vehicles like Youtube and social media to communicate to a new generation of physicians and the public. He also cited evidence that physicians who'd had genetic testing themselves were 8 times more likely to order genetic tests for their patients. Participants discussed "alert fatigue", where overwhelming people with materials (in this case, physicians with EMR alerts) could dissuade them from using it when they only want the most critical details. The green movement making systems paperless may also encourage more alternative methods of displaying information. Genetics classes could also be more multidisciplinary.

Outcomes measurement *Michael Murray*

Michael discussed what outcomes current projects should focus on. Currently, most projects focus on health outcomes, medication compliance, and decreased costs. For WGS, clinical time spent and downstream costs are also important. Preemptive DNA testing could overly worry patients and cause them to take unnecessary genetic tests (some of which have been determined to have no benefit), which result in millions of wasted dollars and resources. For the AIDS Clinical Trials Group, data interpretation, payment, and moving between clinical care and research smoothly are all outcomes that need to be addressed. Suggested solutions were holding a summit to assess the needs of payers and providers, figuring out downstream costs, and developing innovation. A summit would also be useful to develop consensus of what sequencing consents should look like. A new frontier in this is surgicogenomics which came out of Geisinger, determining risk alleles that might predict whether to offer surgery or instead use medical management.

Identifying a research strategy for NHGRI and NIH to accelerate clinical implementation (to produce menu of prioritized projects meeting criteria developed above)

Infrastructure Needs:

Databases and central info storage: These can be improved by finding more fully sequenced "controls" to identify SNPs that can be ignored when looking for rare disease-causing variants, possibly from exome projects or large central labs. People who reach extreme old age would also be helpful for looking at protective variants. Allele frequencies would also be a nice statistic to have. Minority populations are also critical to have because they have different allele frequencies. All of this of course is dependent on cost.

Trans-institutional network and CTSA usage: CTSAs tend to get mixed reviews, but having a coordinating center on board already would be helpful. In terms of creating a network, it seems that 90% of the institutions that would normally be asked were present at this meeting, and many groups were also

CTSAs. Having some algorithms and important information available would be helpful for non-members. Groups that could merit inclusion include community health centers, cancer groups, biomarker experts, international groups, health services researchers, and members from the College or Society. A network could also combine its purchasing power for better negotiating positions with sequencing providers.

Production analysis tools for WGS: These could focus on validating false positives and negatives. The CDC just had a meeting on developing standards to be CLIA-compatible in order to move towards clinical validity and utility rather than just analytical validity. NHGRI shouldn't be the only organization overseeing this.

Address potential for WGS costs to outstrip benefits and diminish public support through NHGRI's WGS programs: Utilization could be affected, where WGS is arbitrarily used for many things. HSR community should be engaged because this opportunity should not be lost based on cost-effectiveness.

Hubs for "commodity" genomic medicine services such as affordable WGS, bioinformatics, central "implications" database: Databases need standardization so people don't have to keep recreating modules. NHGRI is organizing a conference to develop an implications database of actionable variants ***(ACTION ITEM)***. The private sector should also be engaged to ensure that we aren't spending federal dollars on things already being done commercially. Already there are many databases of proven SNPs but they're designed for investigators to look up their favorite gene rather than being computer-friendly. Service layers are needed to pull data out for EMR interface and use. Central data collection and storage accessible by everyone is good role for NHGRI. A service where one could upload a sequence and have it analyzed would also be very valuable.

Practical/central support for providers: Paradigm is starting to shift so that non-physicians (pharmacists, nurses, genetic counselors, etc) are having more responsibility. We don't want delivery models to be outdated in terms of workflow by the time we implement them.

Education of patients and providers: Investment in innovative education models is needed, not just defaulting to what we already know. This could possibly be added to goals of the ELSI program.

Develop genomic medicine workforce: We definitely need more bioinformaticists. Genomicists could be represented more in subspecialties (genomic neurologists, nephrologists, etc) to help decision-making. A network of subspeciality fellowships and other early career development might fill this need. Summer programs for medical school students could also urge the importance of genetic research and its role in the cutting edge of medicine.

Policy: Educate the FDA on what genomics is, what is appropriate evidence base.

Research Needs:

Large scale studies to evaluate genomic predictive/diagnostic/prognostic models, include economic assessment: RCTs may be needed for the first few studies as with abacavir, especially for things like common variants as disease predictors, to gain traction in the medical community. Cancer genomimcs has moved forward largely without clinical trials, potentially because of the desperate nature of the disease and lack of viable alternative treatment pathways. Observational models did work with gene systems like KRAS. NHGRI could work on creating a conceptual framework for studies. A variant that seems like it will have a lot of benefit should be the first trial because an unsuccessful trial may hinder

funding and support for future endeavors. NHGRI wants to work with multi-drug, multi-disease variants, but we first need to understand how to integrate factors like the environment, the sum total of variants contributing to a disease, and behavioral changes.

Implementation Strategy/Timeline

Additional Discovery Studies:

One idea was to look at cataloging functional and non-functional elements. Another would be to look at variable penetrance for monogenic diseases, for which a large central database would be useful in order to compile genotypic and phenotypic data and then mine for more knowledge. The HLA locus would also be a good place to look at for adverse reaction studies. Single gene traits like Kabuki syndrome appear to be a valuable model, as does examination of variable penetrance of genes for monogenic diseases, but very large numbers are needed.

Pilot/Demonstration Projects:

Low frequency variants in Biobanks could be considered, although some of these variants have unknown significance. A possible RFA could be made to deal with this in order to study the proteomics of these variants and the pathways that they interfere with. Additional software and analysis tools for WGS and CDS would be helpful. Also, NHGRI should participate in NIH-wide implementation science activities to identify potential genetic/genomic specific findings and disseminate them ***(action)***. A mentoring program could also be established to have experienced implementation centers train less-experienced centers.

Action Items:

1. Ian will send out contact information for all attendees for possible collaboration.

2. NHGRI will look into the trans-NIH dissemination network that Marc Williams mentioned.

3. NHGRI will email everyone about future conference on actionable variants database.

4. Geoff and Teri will develop writing groups and working groups, and at least one manuscript summarizing the colloquium, to be co-authored by colloquium participants.

5. NHGRI will contact attendees about future meetings.