Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio
June 8-9, 2015, Rockville, MD
Executive Summary

The eighth Genomic Medicine Meeting convened leaders in Genomic Medicine to: 1) review NHGRI's genomic medicine portfolio and identify gaps and opportunities for collaborations among them; 2) identify related programs and opportunities for collaborations with NHGRI programs; 3) identify research needs in genomic medicine; 4) enhance approaches to capturing and disseminating best practices for genomic medicine; and 5) examine potential methods for assessing impact of programs.

The meeting focused on six research programs and two meeting-oriented activities of NHGRI, referred to as "Focus Programs": the Undiagnosed Disease Network (UDN), Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT), Clinical Sequencing Exploratory Research Consortium (CSER), Electronic Medical Records and Genomics Network (eMERGE), Implementing Genomics in Practice Network (IGNITE), Clinical Genome Resource (ClinGen), NHGRI Genomic Medicine Meetings and Working Group (GM Mtgs), and the Global Genomic Medicine Collaborative (G2MC), These eight programs, and 22 "Related Programs" relevant to NHGRI's genomic medicine portfolio, were asked to prepare two page summaries of their objectives, organization, and barriers to implementation, available athttp://goo.gl/Td8U11.

Objectives and Barriers in Genomic Medicine
A matrix of objectives related to genomic medicine implementation across the 30 programs was compiled from the program summaries and is available at http://goo.gl/3rL24E. Five objectives were common to four or more Focus Programs: 1) integrating genomic data into patient care; 2) incorporating actionable variants into electronic medical records (EMRs) and developing genomic clinical decision support (CDS); 3) educating clinicians and patients; 4) assessing outcomes of using genomic information in clinical care; and 5) defining and sharing processes of implementation and sustainability.

A similar matrix of barriers (http://goo.gl/yzWkYn) identified four barriers shared by three or more Focus Programs: 1) unclear penetrance of actionable genes; 2) interpretation of variants in ancestrally diverse populations; 3) changes in evidence on importance of variants; and 4) regulations impeding return of results.

Objectives and barriers shared across the 30 programs may identify opportunities for collaborations. For example, several Related Programs share one or more of the five "most common" objectives above, particularly the Air Force Medical Service Personalized Medicine Program (AFMS) and the Institute of Medicine Genomic Roundtable (IOM). These two are in fact actively collaborating with Focus Programs already. Similarly, shared barriers may be best addressed by multi-program collaborations.

Recommendations for Research Needs to be Pursued
Most of the discussion centered on recommendations for research to address barriers and scientific opportunities. These were roughly grouped into six areas as shown below and will be sent to meeting participants to propose prioritization. Recommendations receiving repeated emphasis included:

- Generating evidence
  - Maximize sharing of quality improvement (QI) projects by engaging health systems
  - Establish and maintain a knowledgebase of ongoing genomic medicine studies

- o Measure outcomes of value to patients, clinicians, payers, healthcare delivery systems, providers, regulators, professional societies; involve them in design prior to launching studies
- Data sharing and improved phenotyping
  - o Support standards for phenotype description that are common and comparable across model organisms to humans
  - o Develop patient-oriented ontology and similar tools to facilitate patient-driven efforts
  - o Expand, support, and expect common measures and other program-wide efforts as in IGNITE; include plans to produce program-wide data and common efforts in solicitations
- Identifying and carrying out innovative studies
  - o Engage basic scientists more actively in planning of genomic medicine research programs
  - o Add family history to large-scale sequencing effort to produce > 20K individuals with both, determine when family history adds to or is more useful than sequence information
  - o Study impact and consequences of changes in variant annotation and duty to inform
- Facilitating genomic medicine implementation in the clinic
  - o Create an implementation commons for sharing tools for implementing genomic medicine
  - o Build tools for facilitating ClinVar submissions
  - o Study effectiveness of various clinical reporting formats in improving clinician understanding
- Health disparities and patient engagement
  - o Identify specific health disparities research questions related to genomics
  - o Develop dedicated programs for non-EA populations to fill key gaps
  - o Increase patient engagement in NHGRI genomic medicine programs
- Education and Training
  - o Explore joint training opportunities in genomic medicine with other organizations
  - o Identify and disseminate best practices for clinician education and guidance

The full list of recommendations is available at *[link].*

Collaborations and Next Steps
In addition to recommendations for increased interactions among programs, including use of common elements, multi-program meetings, and involvement of basic scientists in study development and phenotyping ontologies, attendees identified the Patient-Centered Outcomes Research Institute (PCORI) and Genome Canada as key potential collaborators. PCORI would be an excellent partner in developing the patient-oriented ontology described above. Collaborations with Genome Canada and the Canadian Institute for Health Research (CIHR) could help to increase interactions with the Structural Genomics Consortium, GA4GH, and GAPH, perhaps in a joint scientific symposium.

Teri and Howard M. will continue communications with this group and will draft a short (~1,200 words) manuscript with panel members and moderators. Planning will begin for a spring 2016 GMIX meeting to engage basic scientists in functional characterization, nomenclature, phenotyping, and other topics. The possibility of a scientific meeting on genomic medicine implementation will be explored.

The Duke group will circulate the list of recommendations for GMVIII attendees to review and prioritize. Teri will redistribute the GMVIII matrices to the NHGRI genomic medicine programs for updating, to ensure all activities are accounted for and identify activities that are major program emphases.

Welcome, Introductions, and Goals of the Meeting (Howard McLeod, Eric Green)
The major objectives of Genomic Medicine VIII (GMVIII) are to: 1) identify where there are gaps and opportunities to collaborate, 2) look across the NIH Institutes/Centers (ICs) to seek potential partners, and 3) plan for future NHGRI initiatives.

In the past five years, NHGRI has integrated more clinical genomics into its overall Extramural Research Program (ERP). In February 2011, NHGRI published its new strategic plan signaling NHGRI's commitment to bringing genomics into clinical care. The Institute held its first Genomic Medicine meeting in 2011 and has organized seven meetings since, centered on a variety of themes exploring opportunities for genomic medicine implementation.

The Precision Medicine Initiative (PMI) has generated much attention around genomic medicine in government and the media. NHGRI should consider where the PMI will fit into the scope of the ERP. Eric asked GMVIII attendees to help NHGRI prioritize, offer specific suggestions for how to improve its current activities, and give NHGRI visions for new initiatives.

Overview of NHGRI Genomic Medicine Programs (Teri Manolio)
Of the five genomics research domains defined in the 2011 NHGRI Strategic Plan, the two that are most relevant to clinical genomics are "Advancing the Science of Medicine" and "Improving the Effectiveness of Healthcare." At the 2011 Genomic Medicine Colloquium, attending stakeholder groups took stock of existing genomic medicine activities and concluded that many of these efforts were occurring in isolation. This meeting led to a white paper which identified commonalities among these programs and developed an implementation roadmap to share experiences and facilitate adoption.

NHGRI's Division of Policy, Communication, and Education (DPCE) has been active in influencing rapidly changing next-generation sequencing policies of the Centers for Medicare and Medicaid Services (CMS) and U.S. Food and Drug Administration (FDA). DPCE published a guide for investigators on applying for the FDA's investigational device exemptions (IDEs), often needed for clinical sequencing studies. DPCE also now leads NHGRI's clinician education initiative, the Inter-Society Coordinating Committee (ISCC) for Practitioner Education in Genomics, that grew out of the fourth genomic medicine meeting.

Several working groups, workshops, and research programs have formed out of the Genomic Medicine meetings. On a scale of depth of individual patient characterization versus breadth of implementation, the Undiagnosed Disease Network (UDN) and the Newborn Sequencing (NSIGHT) program are mainly focused on in-depth patient characterization. The Clinical Sequencing Exploratory Research (CSER) program has an individual patient focus and also handles broader system issues in multiple clinical settings. The Electronic Medical Records and Genomics (eMERGE) Network has a more systems-based focus in studying implementation in large patient populations. The Implementing Genomics in Practice (IGNITE) Network is designed to study evidence generation and the impact of implementation.

Panel 1 – Key Unaddressed Evidence in Gaps in Implementing Genomic Medicine (Geoff Ginsburg, Jonathan Berg, Pierre Meulien, Gurvaneet Randhawa)
Evidentiary thresholds should be established for deciding whether enough evidence has been generated to justify the pilot implementation of an intervention. Thresholds should also be set for pushing tests into implementation research, and for widespread dissemination and adoption of tests. Mechanisms

are also needed to assess the quality of the evidence generation pipeline and create consensus standard for evidence. In addition, different levels of risk associated with the testing type and the medical context should be considered in developing evidence standards. For example, large-scale genomic screening and tests for selection of expensive molecular therapies should have a higher bar for evidence, while lower thresholds may suffice for optimizing pain control during end-of-life care

Alternatives to studying implementation through randomized controlled trials (RCTs) include learning healthcare delivery systems that can collect real-world outcomes from patients, providers, and other users. Groups such as the Agency for Healthcare Research and Quality (AHRQ) are looking at how ongoing evidence captured through healthcare systems can be incorporated back into a study's research design. Health systems data will be important for comparative-effectiveness research.

Possible opportunities for NHGRI genomic medicine programs include: creating a common measures platform or implementation commons to store lessons learned and implementation guidelines; developing evidence databases or warehouses; working together on joint publications across programs; and engaging the broader stakeholder community. IGNITE has developed a set of common measures that could be adopted by all NHGRI genomic medicine programs to collect evidence data.

NHGRI should consider aligning with the NIH Common Fund Dissemination and Implementation Science initiative to develop training opportunities. NHGRI should also reach out to Affordable Care Organizations (ACOs) as their mandates are to achieve cost neutrality. There might also be opportunities to maximize the impact of quality improvement (QI) projects and educate investigators about how to publish and share data captured through QI projects. To increase the speed of evidence generation, studies should be designed to capture outcomes and have end-users in mind at the outset of implementation research programs.

Payers are motivated by evidence for improved patient outcomes as well as cost-effectiveness. Costs outside of the healthcare system that are associated with healthcare, such as social services, long-term care, and days away from work, should be measured in generating economic evidence. Comparing the costs (including follow-up of incidental findings) of large panel testing, smaller panel testing, and single gene tests will be useful in meeting evidence needs. Incorporating evidence into practice guidelines would also inform insurers and speed adoption as insurers often base their decisions on guidelines.

Many commercial firms are not collecting enough surveillance data on tests post-marketing, especially vendors marketing different forms of cancer profiling. This has led to variability in precision oncology databases. A pharmacovigilance project could be supported through the PMI to provide needed data.

Panel 2: Consistency of Interpretation of Variants Across Expert Labs / Groups, ClinVar Submissions (Dan Roden, Gail Jarvik, Robert Green)
Concordance across expert labs is challenging. Comparing variant classifications at multiple CSER sites to the ACMG standard variant classifications produced a 73% discordance, with ACMG tending to categorize discordant variants as variants of unknown significance (VUS) rather than definitively benign or pathogenic. When all CSER labs adopted ACMG criteria, concordance among them increased. A lack of infrastructure and resources for variant assessment (including large publically available datasets) was identified as a major hurdle to consistent interpretation. NHGRI should work with clinical companies to develop a broader data commons to facilitate sharing their genomic data and improving interpretation.

ClinGen is developing a curation interface for groups to test methods to improve consistency of clinical interpretation and explore creating expert consensus. ClinGen is proposing rules to define what genes should be included in different clinical tests. Basic scientists should be engaged in variant classification curation, potentially by attending ClinGen or ClinVar meetings. NHGRI should consider engaging CMS to explore opportunities to work on coverage with evidence development (CED) studies.

Convening groups such as professional societies and commercial entities will be important to ensure consensus in interpreting genetic test results. Sharing experience and evidence will help in resolving discrepancies in interpretation. Re-engaging patients via email for assessing phenotypic manifestations of unknown variants might also be an effective and low-cost method to assist in resolving variants. ClinVar should create an infrastructure to support both a variant-centric and a case-centric database. NHGRI should support research on determining the best structure for a classification knowledgebase.

Panel 3: Changes in Evidence and Updating Clinical Recommendations (Howard Jacob, Heidi Rehm, Sharon Plon, Katrina Goddard)
Companion diagnostics rely on specific methods to detect mutations and generally focus on a limited number of approved mutations with the strongest evidence for efficacy. Research should be developed to discover mutations that convey response as well as resistance to new drugs and drugs off patent. In the future, a patient's clinical genome data might be stored in the EHR to be used for companion diagnostics, when new medications are prescribed, and when guidelines have changed for a patient's existing medications. There may be issues with FDA approval for using the clinical genome in this way.

To enable re-analysis of patients' genomic data, mechanisms are needed for long-term storage of the variant data taking into account costs of re-sequencing vs. re-analysis. As resolution improves for next-generation data, re-sequencing may be more informative than re-analyzing older raw data. Guidelines are needed for what changes to a patient's genomic data will require re-contact and re-reporting and how these changed interpretations will be delivered to patients and their providers. Clinical trial-type studies should be developed to study return of changed classification results and the duty to inform in multiple settings such as rare diseases, cancer, and healthy patients.

NHGRI genomic medicine programs vary in the numbers of genes they return to patients, from single-gene results in one IGNITE study to 5,000 genes in a CSER study. CSER has demonstrated the possibility of achieving, in a research setting, an acceptable cost per quality-adjusted life-year (QALY) gained for several panel tests compared to standard of care. CSER has also learned that individual preferences for information may change over time and with varying circumstances even if the interpretation has not changed. If there are changes in interpretation, patients' individual perspectives and preferences should be considered, and specifically what they might be interested in being re-contacted about.

Unique healthcare identifier numbers will be critical in implementing screening initiatives and obtaining long-term data. Genomic medicine should look to sources such as e-commerce sites and grocery stores, for examples of how to handle dynamic data and use them to assess and influence health behaviors.

Indication-based testing should be compared to broader testing, or a system using both, on value in both clinical care and research. Health systems are reluctant to use broader panels, to avoid incidental findings needing follow up, but might be willing to collaborate with NHGRI in this research. Cost data can be collected from laboratories that are assaying more variants or genes than were ordered. As VUS are typically not reported or followed up on, it would be useful to randomize patients to have VUS results returned to assess the downstream costs and impact of returning VUS to patients.

The UDN found that clinical sites strongly preferred to have whole genome sequencing (WGS) data at the outset rather than generating exome data first and then ordering WGS if the causal variant is not found, but this may reflect the research orientation of these sites. This should be further studied, and education around dealing with results from larger panels should be developed for physicians.

Panel 4: Metrics of Progress and Measures of Impact Including Cost-Effectiveness, Outcomes to Value to Players, Influencing Quality of Care Through Healthcare Systems (Marc Williams, Warwick Anderson, Erwin Bottinger, Ruth Brenner, Howard McLeod)
Standardized common outcome measures such as those being considered in IGNITE would help to combine evidence generated by NHGRI programs. NHGRI should measure outcomes of value to patients, payers, healthcare delivery system, and regulators. Although NHGRI programs' EHR working groups have come together and have produced joint publications, data harmonization is still a major barrier to merging outcomes data. It would be useful to incorporate a component of sharing common measures among other NHGRI-supported programs into RFAs, especially those for coordinating centers. Programs can then set aside funds specifically for network-wide and inter-program projects.

In dealing with issues of reimbursement policies and engaging with payers, the GMWG has been connecting with the Health Care Systems Research Network (HSCRN; formerly HMORN) to explore opportunities to collaborate on evidence-generation projects. NHGRI genomic medicine programs should build a larger evidence base for the value of single-gene testing vs. larger panels.

Learning healthcare systems rely on large databases of information gleaned from patients to inform clinical decisions and improve healthcare for future patients. Developing and sharing existing tools, like decision support rules and phenotyping algorithms, will be critical in helping healthcare systems become genomics-enabled learning healthcare systems.

Metrics for success of implementation success vary among different stakeholders. In oncology, payers are focused on whether a somatic sequence will change a medical decision, almost independent of patient survival, while patients are understandably more concerned with health outcomes. Multiple communities, including clinical pharmacology, clinical genomics, and professional societies, should be convened to create guidelines with credibility across multiple constituencies, despite challenging legal and administrative hurdles. Compilations of genomics-oriented guidelines such as those being developed by NCBI's MedGen and the Genetic Testing Registry will be helpful in this regard. It will be important to find out why physicians choose to adopt some expert guidelines and reject others, and how this differs by specialty. Research is needed on what non-geneticist physicians know about genetic testing, what guidelines they follow, and what recommendations they have adopted in clinical practice.

Panel 5: Enhancing Functionality of EHRs for Genomic Research, Including E-Phenotyping, Integrating Genomic Data, Transportable CDS, Privacy Threats (Rex Chisholm, Alexa McCray, Chris Chute)
NHGRI should conduct research on best practices for sharing CDS rules and creating tags for actionable variants that multiple CDS systems can fire off of. Although interoperability of CDS rules is still an obstacle, eMERGE is launching a CDS rule repository that will contain visual logic of how a CDS rule might be fired. ClinGen, ClinVar, and CPIC have been normalizing forms of CDS rules. NHGRI should leverage genomic characterization methods and data elements from the clinical informatics realm.

Standardization of APIs that are executable in an EMR-agnostic fashion will be needed to achieve large-scale implementation. In developing standards for collecting health data, ClinGen's GenomeConnect platform may provide a model for extracting health data directly from patients and tying into the Human

Phenotype Ontology (HPO) if extracting them from EHRs is problematic. Research is needed around best methods for transferring data from external storage to close-to-compute status for analysis, particularly to refine variant calling and sequence alignment mechanisms.

To improve consistency of phenotyping, NHGRI should consider leading a trans-NIH project to pool different ICs' standards for phenotyping. It would also be useful to assess whether more granular phenotyping incrementally increases the power of PheWAS studies. Large numbers are important in studying common variants, but phenotypic detail is important for WGS and targeted sequencing, particularly in studying rare variants.

How patient data can be sustainably integrated and de-fragmented across different providers (such as hospitals, pharmacies, claims data) should also be considered. Sufficient metadata on the provenance of these data, and encryption of metadata to protect privacy, will be important. Metadata should not be separated from genomic data. Who will have ownership of these data should also be considered, as vulnerable populations might not benefit from a more open model of sharing personal health data. In addition, many people do not have the capability to own and manipulate their raw genomic data files.

Training in clinical informatics subspecialties such as health IT and EHR systems is available through programs like the National Library of Medicine (NLM) informatics fellowships/training programs. In addition, ACMG and the American Medical Informatics Association (AMIA) have been discussing a clinical informatics fellowship program with an emphasis on genomics. NHGRI can convene these groups and others developing training programs to ensure the harmonization of foundational concepts.

The Global Alliance for Genomics and Health (GA4GH) is exploring data standards and should be encouraged by NHGRI and Genome Canada to look at current standards before reinventing the wheel. IOM's Displaying and Integrating Genetic Information Through the EHR (DIGITizE) Action Collaborative has been working to represent genomic data in the EHR, building off of existing HL7 standards 2.5.1.

Phenotyping should be interoperable, dynamically searchable, and expanded beyond binary phenotypes. Mobile health and digital platforms are now adding to the complexity of phenotypes and allow collection of more dynamic phenotypic information as opposed to static measures. NHGRI should consider projects on the integration of genomic information into mobile health technologies. The meaning of a "phenotype" should be informed by data on humans data as well as model organisms. Groups like HPO and Monarch that are developing principles for phenotyping ontologies learned from model organisms should collaborate with NHGRI programs to determine how best to capture phenotypes. NHGRI should think about implementing transportable phenotyping algorithms developed in eMERGE across other NHGRI genomic medicine programs such as IGNITE and CSER.

Panel 6: Increasing Diversity Among Patient Populations and Care Systems (Carol Bult, Cynthia Powell, Vence Bonham, and Craig Hanis)
Barriers to increasing diversity in clinical research include physician attitudes about race and ethnicity; patients' mistrust of research; lack of involvement of minority investigators, physicians, and community stakeholders; language barriers; lack of awareness among clinicians and patients about clinical studies; lack of time to participate; lack of access to research infrastructure and technology; and geographic distance to medical research centers. In addition, the lack of data on non-European ancestry (EA) populations and the limited ability to interpret data on human variation are disincentives for studying underrepresented groups. Addressing disparities and expanding non-EA knowledgebases are becoming critically important, especially in pediatrics where non-EA participants now form the majority.

Well-resourced medical research centers in higher socioeconomic areas have a more even balance of racial, ethnic, and gender diversity than centers located in less advantaged areas. Clinicians in medical centers serving diverse populations should also be diverse. Researchers should make ties within the community, as through community advisory and outreach boards, to inform patients about studies and help them understand why this research is important to them and to their communities. Participants should be involved in developing consent forms to increase their relevance. Partnering with faith-based organizations can also be critical in developing community-centered programs and gaining trust.

NIH and NHGRI initiatives to increase diversity in the biomedical workforce continue to be needed. Diversity of post-docs and faculty should be maintained by providing supportive environments and establishing effective mentoring teams. Developing supplements and incorporating diversity studies into RFAs might incentivize research programs to identify the best strategies for engaging diverse communities. NHGRI should also develop projects such as PAGE that study only all non-EA populations.

First Day Summary
Panel 1 – Evidence Gaps: NHGRI should share the message with payers that "implementation is needed to generate evidence, and evidence is needed to support implementation." NHGRI should also influence or form a partnership with the FDA to undertake a genomic medicine surveillance system to capture data as tests are marketed, similar to their medical device surveillance system.

To maximize the use of data generated through QI projects, a repository should systematically collect and store different QI methods. NHGRI and HCSRN can work together to teach researchers how to use a QI approach to generate and publish evidence. NHGRI should also consider ways to demonstrate the scientific value of QI methods and outcomes to more basic researchers.

Panel 2 – Consistency of Interpretation: NHGRI should engage basic scientists more in designing research for variant interpretation. NHGRI might consider partnering with payers for coverage with evidence development (CED) studies rather than focusing solely on CMS for such work. Although there are legal barriers to multiple payers collaborating in coverage evaluation efforts, there might be opportunities to work with integrated health systems in which payers are part of the systems. Implementation researchers at large institutions should share their strategies for engaging payers. NHGRI should also consider models similar to cooperative oncology groups in genomic implementation.

Panel 3 – Evidence Changes: NHGRI should collaborate with other NIH ICs to conduct studies demonstrating the added value of WGS compared to limited testing. NHGRI should also support research around crowd-sourcing for assessing actionability of rare variants and for finding cause and treatment. NHGRI should support development of a parent-oriented ontology for patients to write in their data in ways that they see and know. This can be raised with PCORI.

Panel 4 – Metrics of Progress and Impact: It will be important to identify and measure outcomes that are of value to different stakeholders, not necessarily only those that are most publishable. Systems might also be designed to guide clinicians to specific tests using automated tools or a genome consult service. NHGRI should construct an implementation commons for sharing tools and language, challenges and solutions for overcoming them, and outcomes in clinical implementation. NHGRI should convene a regular meeting of all NHGRI programs to discuss their projects and identify areas of synergy. NHGRI should look outside of traditional cost utility measures such as quality of life and identify patient-oriented measures, such as the value of the reduction of uncertainty that comes with a diagnosis.

Panel 5 – Functionality of EHRs for Genomics Research: NHGRI should engage trainees in NHGRI genomic medicine programs by developing small projects for fellows to solve thorny problems using informatics. NHGRI might also consider developing research around deciding when a phenotype measure is superior to (or adds to) the genotype. The importance of precise phenotyping may vary depending on the frequency of the variant, and may be particularly important for rare, highly penetrant variants with disproportionately large effects on a complex phenotype. NHGRI should support research to determine the value of deep phenotyping, including related and secondary phenotypes, and identify the minimum level of phenotyping to generate robust findings in studying rare and common variants.

Panel 6 – Increasing Diversity: NHGRI should identify specific health disparities related to genomics to study in a variety of ways, including increased representation of non-EA populations. Studying diverse populations is particularly important in pediatrics as the proportion of pediatric patients who are minorities continues to increase. Community advisory boards should be given a strong voice to ensure that their perspectives are heard. NHGRI should also identify what characteristics of genomics would be particularly important to highlight in attracting non-EA trainees to the workforce.

Second Day Review of First Day Discussions
NHGRI should consider investing in cellular phenotyping methods that will enable deep, definitive functional characterization of variants. Some groups are doing innovative work in functional validation of Mendelian-like, protein-altering variants, but gene discovery studies still outpace research to understand all of the variation in a gene that is already known to be involved in disease.

The term "deep phenotyping" is used in multiple ways, with one definition encompassing the understanding of the disease mechanism, from gene signal to the full translational pathway, to find targets for new drugs or new molecular diagnostics. Others define deep phenotyping as the association between a genetic variant and characteristics in the EHR. The group agreed that deep phenotyping should be used to define subtypes of disease that are definable, reproducible, and therapeutically relevant, and that granularity of phenotyping whether molecular, physiologic, or clinical, will be increasingly important. It might be useful to work with the Toronto Hospital for Sick Children which is putting in place a new platform for phenomics studies.

There are opportunities for NHGRI to annotate non-DNA biological specimens and establish standards for data formats. NHGRI might help identify a standard set of biological specimens to be collected for different phenotypes and consider how and when to draw these samples to maximize their value.

The genomics community should explore ways to prioritize associations to pursue for functional characterization. For genes already implicated in disease, more interrogation of relevant pedigrees could efficiently identify additional mutations for functional characterization. Genes with mutations that can be semi-tolerated with appropriate treatment should be prioritized, and basic scientists should also be engaged in efforts at functional characterization.

As NHGRI collects more individuals' sequences, it might be possible to identify variants that basic biologists can study using knockout techniques or CRISPR. NHGRI should identify, incentivize and engage expert groups to develop tools to scale up functional characterization. NHGRI should consider aligning with the Rare Diseases Research Catalyst Network assembled by CIHR and Genome Canada which is bringing together basic scientists working with model organisms for functional studies.

To facilitate interactions among basic science and clinical research groups, GMWG should organize a series of scientific meetings devoted to sharing of information in a scientific forum, similar to a Keystone Meeting. GMWG would invite basic scientists doing work that they believe has clinical applications and clinical researchers with research questions that they can use basic scientists' help with, perhaps with different thematic emphases such as phenotyping or function. NHGRI should also encourage investigators from the different genomic medicine programs to attend other programs' meetings.

A post-meeting survey of attendees would be helpful in prioritizing recommendations from GMVIII.

Panel 7: Streamline Clinical Workflow, Transportability to Other Systems (Howard McLeod, Mike Gaziano, Erin Ramos, Stephen Kingsmore)
A barrier to transporting knowledge across systems is that curation of data is unique to each institution's EHR system, even among EHR systems with the same vendor. There have been few practical analytics to aid in the use of EHR data and very little investment in EHR mapping. There is also variability in the way clinical groups use ICD codes. Clinical workflow is a local issue that is unlikely to have a generalizable solution. Developing tools that allow physicians to manage data in real time and in a time-efficient manner will help alleviate local workflow issues.

NHGRI should pursue standardizing nomenclature for genomic variation to be inserted into the clinical process with input from HL7, IOM, and similar groups. NHGRI should consider exploring diagnosis codes for genetic conditions, as even common genetic conditions such as Lynch syndrome do not have specific diagnosis codes. NHGRI should also work with other NIH ICs to assist in creating EHR-computable phenotype definitions, and activities around transportability should be broadened. It might be possible for NHGRI and/or the PMI to build a business case demonstrating why EHR vendors and other industries should invest in genomics tools and interoperability with other EHR vendors' systems. EHR vendors are waiting for the genomics research community to teach them how to implement these tools. A good way to engage EHR vendors would be to present automated tools developed by NHGRI genomic medicine programs that insert genomic information into the clinical decision-making process.

It might be possible to partner with ACMG, AMIA, and NLM to develop training opportunities for EHR scientists, potentially by designing a K01, K08, or T32 training programs. In addition, practitioners should be educated on how to enter data into EHR systems to facilitate their use for research.

Panel 8: Clinician Education (Especially Residents on Rotation, Genetic Counselors), Reporting Results to Clinicians (Mary Relling, Julie Johnson, Bob Wildin, Wendy Rubinstein)
Terms should be standardized to convey high-risk status to providers and patients. In response to vendors asking the genomics community to standardize CDS terms, CPIC is creating gene/drug clinical guidelines and publishes its guidelines widely to solicit and incorporate feedback from the community.

Improving clinical reports for physicians might minimize the need for specific education programs. Specially designed reports with safety notes, visuals, and checklists will be helpful to guide non-geneticist physicians. Programs that are creating clinical reports should compare their pipelines to determine the most useful formats and content.

Physicians should also be taught when to refer to the appropriate specialists. Research is needed to determine which clinical contexts require clinicians and laboratories to interact on interpretations. IGNITE and other programs might be able to study how frequently Infobuttons are helpful in guiding physicians to correctly order a test. It might also be possible to work with SimulConsult, a service that

provides decision support for providers that includes a differential diagnosis and helps clinicians decide which test to order. NHGRI should consider partnering with direct-to-consumer (DTC) companies in providing education to help physicians interpret and convey DTC test results to patients.

ISCC should collaborate with other NHGRI programs' education working groups and may also be well positioned to teach providers how they can help with phenotyping. In introducing genomic medicine to non-geneticist physicians, it will be important to find local champions. who do not need to be board-certified geneticists. It might be possible to work with groups like ACMG and the American Board of Medical Specialties (ABMS) to develop a genomic medicine certification curriculum for non-geneticist physicians. International groups developing education around genomic medicine should also be sought out, such as the Master's in Genomic Medicine being launched by the UK National Health Service.

Surprisingly, some groups have found that younger clinicians were less willing to embrace genomic medicine testing than more senior clinicians. To increase relevance to residents, materials on genetics and genomics should be included on board exams. There is a need to attract students to the medical genetics field as 50% of available slots in medical genetics residency programs go unfilled each year. New and larger genetic counseling training programs are also increasingly needed.

Panel 9: Patient facing information tools, counseling/consent, reporting results to patients (Laura Lyman Rodriguez, Steve Joffe, William Lawrence, Janet Williams)
A strategically designed, evidence based suite of patient-facing tools should be implemented in healthcare systems, especially those without access to genetics/genomics experts, to educate patients about the implications of testing and test results, assess risk by collecting patient phenotypes and family history, and support patients in making decisions about ordering the test and potential interventions.

Existing patient-oriented resources provide information on specific diseases but are not personalized tools to help patients understand if they should seek genomic testing, how it might benefit their family, and how they can communicate this information with their families. Evaluation of communication methods and assessing their impact on patient outcomes will be critical to pursue. The International Patient Decision Aid Standards group should be engaged to support studies evaluating the impact of patient-facing information on patients' health, longevity, or other relevant outcomes. NHGRI should develop a repository for decision-making tools and should decide who will maintain and update them. To increase patient engagement, participants should be involved as partners early on in putting together research plans, writing consent forms, and assisting with community outreach. It was proposed that patients should have access to their own results from the studies in which they participate.

Patients have advocated for patient reports to be designed to be shared with patients' providers as well as family, friends, and schools. Patient reports should have understandable language, logical flow, visual appeal, information on what to expect in the future, and possible next steps. There should also be different options for receiving reports, as through patient portals, flash drives, phone apps, etc. NHGRI programs should collect and evaluate qualitative data on patients' experiences and preferences for how genomic information is communicated to them. NHGRI should support research on education and how genomics should be communicated to different audiences, and should collaborate with expert groups in communication and decision-making sciences to determine what some of the key endpoints should be.

Although standardizing consent for genome sequencing would be useful, there are differences between consent for research and consent for clinical care. Consent should be dynamic, recognizing that a patient's or family's preferences for receiving information might change over time. NHGRI also should

study informed consent and decision-making in the public health setting around parents allowing researchers to use their children's dried blood spots for research. Work is still needed in assessing genomic literacy in different ways and in different populations. NHGRI educational tools for the public might be made more of an interactive platform by enabling a bidirectional flow of information. Individual sites and programs within the NHGRI genomic medicine portfolio should share their patient engagement experiences broadly and adopt and evaluate more systematic approaches to engaging patients as partners rather than subjects in research. PCORI's engagement rubric document provides specific examples of how groups have engaged patients in research.

Second Day Summary and Discussion (Teri Manolio, Howard McLeod)
Slides summarizing each panel's recommendations were discussed and are attached. Revisions during discussion are shown in yellow and high-priority recommendations are in blue. Below are summarized only the key additional discussion points, particularly for panels 1-6 discussed at the end of day 1.

Panel 1 – Evidence Gaps: NHGRI's programs should identify types of evidence to collect and share and develop collaborative projects with other genomic medicine groups, including Genome Canada.

Panel 2 – Consistency of Interpretation: NHGRI should consider setting conditions for a "safe harbor" to allow sharing of data among programs under a consensus set of regulations, policies, and procedures, potentially through the FISMA certification process. It might be possible for dbGaP to indicate when additional phenotypic data are available for a particular dataset. Before attempting to establish standards for phenotype collection, NHGRI and the genomics community should consider creative methods of engaging patients, such as the Platform for Engaging Everyone Responsibly (PEER), wearable technologies, PCORI activities, and DTC gamification. NHGRI should consider studying what would be the minimum amount of phenotypic data needed for specific studies. NHGRI might consider a project to collect family health history (FHH) information on 20K sequenced people and examine how FHH informs the sequence data and vice versa. FHH can be readily added to existing projects and stored as closely as a possible to the sequence data.

The ninth Genomic Medicine meeting (GMIX) can bring together basic and clinical investigators to focus on sharing phenotypes and structuring the data to be computable. Examples of fruitful basic science-clinical collaborations can be presented to show how to connect basic science and clinical research. Discussion is also needed about the importance of speeding interpretation of variants to a pace that benefits the patients. Industry should also be represented to involve them in early clinical discovery.

Panel 3 – Evidence Changes: In recognizing the dynamic nature of genomic data, existing sequencing studies should assess the impact on patients and providers of changing annotations and interpretations. Non-geneticists might be queried on whether and how updated annotations increase or decrease their confidence and adoption of genomic medicine in general.

Panels 4-6: There were no changes to the summary slides for Panel 4 (Metrics of Progress and Impact), Panel 5 (Functionality of EHRs for Genomics Research) and Panel 6 (Increasing Diversity).

Panel 7 – Clinical Workflow: NHGRI can contribute to standardizing EHR-computable human allelic nomenclature, in collaboration with model organism nomenclature groups. The CDC has assembled experts from CPIC, PharmGKB, and other groups to address the lack of nomenclature standards in pharmacogenomics. Standard nomenclature would help document what test was done and what it was and was not capable of detecting, as it is not always clear what a test might have missed. It should be

recognized that physicians can handle quantitative data, and labs should consider this before making decisions on whether to leave out important quantitative information from the results.

It might be possible for NHGRI to set standards of care for test results turnaround time. NHGRI should establish an ideal and then decide what is feasible when also taking into account the acuteness of the clinical scenario, workflow, and the balance of cost and accuracy. A possible ideal is to have the genome sequence data already generated and available for re-interpretation.

NHGRI should collaborate with groups like the NLM and the NIH Big Data to Knowledge initiative, as well as ACMG, AMIA, and the American Society of Human Genetics (ASHG) to explore specific joint training opportunities in informatics and EHR. Marc Williams, Bob Freimuth, and Alexa McCray (NLM) will be working on this and will provide updates on their progress at an upcoming GMWG meeting.

NHGRI should promote software development for presenting genomics to clinicians; focus on tools that are transportable across multiple settings; facilitate ClinVar submissions by working with ClinVar and NCBI to leverage laboratory workflow; provide groundwork for new entrants to genomic medicine by identifying the necessary tools, knowledge, and components used for clinical implementation at more expert settings; and build better business cases for EHR vendors to incorporate genomic information. NHGRI should also examine areas where research can point industry toward solving these problems.

Panel 8 – Clinical Education: ISCC and NHGRI should consider working with the UK NHS Genomics Education program to identify possible. NHGRI should consider developing or encouraging other groups to develop a Master's in Genomic Medicine or similar certification to teach clinicians how to provide valuable consultation without being a board-certified geneticist.

NHGRI should collect data from implementing clinical sequencing on a small scale (~500 participants a year) and compare outcomes across the NHGRI genomic medicine programs. A clearinghouse of approaches, tools, and best practices used by all NHGRI genomic medicine programs to enable testing of generalizability among these programs would also be useful. NHGRI should explore how to empower and provide evidence for appropriate billing of genetic counseling services.

NHGRI, IOM, and other groups should interact with the knowledge vendors supplying information for CDS tools like Infobuttons. It will be important to see what the knowledge vendors' best practices are for collecting and utilizing information that research community generates. NHGRI should discuss how to manage affiliate members, project not funded by NHGRI but agreeing to collaborate, across the NHGRI genomic medicine portfolio to promote broader dissemination of their tools and deliverables.

Physicians and medical specialties might be more motivated by patient advocacy groups voicing concern that their physicians do not know about particular genetic conditions than by evidence and use cases provided by implementation researchers. NHGRI should survey patients to ask them what they want their physicians to know about genetics.

NHGRI should also develop ways for healthcare systems to systematically collect information from local end-users about their specific genomics needs. NHGRI should also develop education for clinicians around when to order tests. A first step might be for the GMWG to invite SimulConsult investigators to report on their experiences. Infobuttons can also be used to assist in lab ordering.

Panel 9 – Patient-Facing Information Tools: NHGRI genomic medicine programs should support more work in patient engagement and collect data on local patient engagement experiences systematically. NHGRI should also develop and evaluate tools in clinical settings. It would also be useful to look across the NHGRI genomic medicine portfolio to evaluate participant access to data.

As NHGRI genomic medicine programs are renewed and reconfigured, NHGRI should charge these programs to recognize the missions of other programs and propose inter-program common measures and collaborative projects across more than two at a time. Monthly or quarterly meetings among NHGRI genomic medicine programs' leaders might be useful. Formal working groups should be formed for truly cross-cutting topics like EHR, informed consent, actionability, and other listed in the GMVIII matrices. It might also be possible to webex and record meetings for broader reference.

Collaborations and Next Steps

Multiple collaborative opportunities were identified and PCORI and Genome Canada were cited as key potential collaborators. PCORI would be an excellent partner for increasing patient engagement and conducting comparative effectiveness research. Collaborations with Genome Canada and the Canadian Institute for Health Research (CIHR) could help to increase interactions with the Structural Genomics Consortium of the Universities of Toronto and Oxford, with GA4GH to utilize existing APIs and other resources in developing health data standards, and with GAPH for a joint scientific symposium.

Teri and Howard M. will continue communications with this group and will draft a short (~1,200 words) manuscript. Panel members and moderators would be co-authors on the white paper if this is permitted by the journal. Planning will begin for a spring 2016 GMIX meeting to engage basic scientists in functional characterization, nomenclature, phenotyping, and other topics. A scientific meeting on genomic medicine implementation such as a Keystone or Gordon conference will be explored.

The Duke group will circulate the list of recommendations for GMVIII attendees to review and prioritize. Teri will redistribute the GMVIII matrices to the NHGRI genomic medicine programs for updating, to ensure all activities are accounted for and identify activities that are major program emphases.

Attachments:
1. Recommendations for potential NHGRI-led efforts, 7/24/15
2. Matrix of objectives of major genomic medicine programs, 7/24/15
3. Matrix of barriers to genomic medicine implementation, 7/24/15

Genomic Medicine Meeting VIII (GM8) Recommendations for Potential National Human Genome Research Institute (NHGRI)-Led Efforts, 7/24/15

Generating evidence

1. Maximize sharing of quality improvement (QI) projects, engage health systems such as the Health Care Systems Research Network (HCSRN, formerly the Health Maintenance Organization Research Network or HMORN) to bring QI projects together
2. Identify types of evidence (and goals they support) to collect and share across programs
3. Identify payers' needs for evidence across diverse payers, integrate with HCSRN and America's Health Insurance Plans (AHIP)
4. Conduct post-marketing studies of genetic testing similar to pharmacovigilance studies, for outcomes of testing, collect data directly from patients, or possibly registries
5. Establish and maintain knowledgebase of ongoing genomic medicine studies
6. Facilitate coverage with evidence development studies through payers
7. Measure outcomes of value to patients, clinicians, payers, healthcare delivery systems, providers, regulators, professional societies (for developing guidelines); involve them in design prior to launching studies

Data sharing and improved phenotyping

8. Provide structure and guidelines for sharing phenotypes (similar to those for sharing genotypes)
9. Support standards for phenotype description that are common and comparable across model organisms to humans
10. Explore/exploit potential of crowd-sourcing for assessing phenotypic manifestations and actionability among individuals carrying rare variants
11. Enhance approaches for patients to phenotype themselves using standardized terms; develop patient-oriented ontology and similar tools to facilitate patient-driven, crowd-sourcing efforts for finding disease causal variants and potential treatments
12. Expand, support, and expect common measures and other program-wide efforts as in Implementing Genomics in Practice (IGNITE); include plans to produce program-wide data and common efforts in solicitations
13. Encourage agreed-upon nomenclature, variant definitions, and unique identifiers (allele registry) such as pharmacogenomic "star" alleles, needed for computing by clinical decision support (CDS) systems

Identifying and carrying out innovative studies

14. Engage basic scientists more actively in program planning, learn what challenging clinical questions are being faced
15. Consider "cooperative sequencing groups" like Cooperative Oncology Groups allowing rapid entry into studies
16. Add family history tool to large-scale sequencing effort to produce > 20K individuals with both, determine when family history (FHx) adds to or more useful than sequence information

17. Accelerate rapid genotype-phenotype explorations at speed that would benefit patients
18. Study impact and consequences of changes in variant annotation and duty to inform in rare disease, cancer, healthy patients
19. Conduct clinical trials of added value of whole genome sequencing to more limited testing taking cost of testing and follow-up into consideration
20. Determine when phenotype measures such as biochemical assays are superior to (or add to) genotype as with *TPMT, HFE*

Facilitating genomic medicine implementation in the clinic

21. Create "computable" guidelines that can be readily integrated with CDS systems if possible
22. Design systems to guide clinician to specific genomic test to order (in addition to how to use result), conduct necessary research to determine when and how best to do that
23. Promote software development for presenting genomics to clinicians
24. Create an implementation commons for sharing of tools and data supporting genomic medicine implementation projects
25. Ensure sequencing data never separated from meta-data or their provenance data and consent levels, what was tested, what could and couldn't be detected
26. Build tools for facilitating ClinVar submissions
27. Assist new entrants to genomic medicine implementation by building on tools and knowledge from more expert settings
28. Build better business case for EHR vendors to incorporate genomic information, perhaps modeled on other National Institutes of Health (NIH) health economics-focused efforts
29. Embrace affiliate/associate models to participate in ongoing genomic medicine programs
30. Enhance portability and interoperability of e-phenotypes and genomic related clinical decision support (gCDS) algorithms and study impact; provide logic structure for CDS rule to be coded
31. Integrate tool development into funded implementation projects, ensure clinical tools are developed and evaluated in clinical settings
32. Compare and unify sequencing clinical reports from major clinical sequencing labs, consider bake-off of data comparability
33. Study effectiveness of various clinical reporting formats in clinician understanding and subsequent action

Health disparities and patient engagement

34. Identify specific health disparities research questions related to genomics
35. Promote synergism among multiple diversity efforts NIH-wide
36. Use mobile technologies to overcome information technology IT barriers in under-served populations
37. Develop better methods to utilize genomes from different ethnic groups for discovery and interpretation
38. Involve community advisory boards from beginning of study design, give freedom to push back with investigators when needed

39. Develop dedicated programs for non-EA populations to fill key gaps
40. Increase patient engagement in NHGRI genomic medicine programs
41. Ensure patient access to their genomic data at levels they specify and desire

Education and Training

42. Compare and identify most effective ways for clinicians to understand meaning of variants especially Variant of Uncertain Significance (VUS)
43. Assess and improve effectiveness and understandability of genetic test reports by diverse medical practitioners
44. Examine impact of adding genome consult service (like radiologists) on clinicians' understanding and appropriate use of genomic findings
45. Engage trainees in the multiple electronic health record (EHR)/informatics training programs in addressing e-phenotyping and CDS problems in genomic medicine
46. Explore joint training opportunities in genomic medicine with American College of Medical Genetics (ACMG), American Medical Informatics Association (AMIA), American Society of Human Genetics (ASHG), NIH Big Data to Knowledge Initiative (BD2K), National Library of Medicine (NLM)
47. Partner with Genomics England effort spending £20M for clinician education, learn from, borrow materials
48. Consider supporting certificate program for non-geneticists – estimate/document the need
49. Identify and disseminate best practices for clinician education and guidance including InfoButton (context-sensitive links embedded in EHR systems) and underlying knowledge bases
50. Partner with 23AndMe in funding education around providers presented with direct-to-consumer (DTC) results
51. Support training in communication science for genomic medicine trainees
52. Support research to identify why some clinicians are more accepting of genomic medicine than others

Objectives of major genomic medicine programs related to implementation of genomic medicine; "XX" indicates major focus of program.

Objectives Related to Genomic Medicine Implementation	Focus Programs								Related Programs										
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	AFMS	CMG	CPIC	GA4GH	GAPH	GTEx	IOM	ISCC	LSAC	PAGE	PhenX
Improve genomic diagnostic methods	XX	X	X							X									
Facilitate research in undiagnosed and/or Mendelian diseases	XX	X	X							X				X					
Investigate the use of genomic data in newborn care		X																	
Research ethical/legal/social issues in genome sequencing		XX	X	X											X				
Interpret sequence data in variety of clinical/publ hlth contexts		XX	X	X															
Integrate genomic data into patient care	X	X	X	X	XX				X						X				
Incorporate actionable variants into EMR, develop CDS	X	X	X	X	XX				X						X				
Educate clinicians and patients on genomics in clinical care			X	X	X	X		X	X		X				X	X			X
Develop electronic phenotypes				X															X
Identify variants related to complex traits	X		X	X										X				X	X
Characterize pharmacogenetic variants and use in care				X	X						X								
Assess outcomes of using genomic information in clinical care		X	X	X	XX				X					X					
Assess penetrance of potentially actionable variants				X															
Translate implementation outside highly specialized centers	X		X		XX	X													
Define and share processes of implementation, sustainability	XX	X	X	X	XX		X	X							X				
Share genotype/phenotype info through open databases	X	X				X						X							
Standardize clinical annotation and interpretation			X			XX													X
Improve understanding of variation in diverse populations			X	X		X								X				X	
Assess actionability of genes and variants for clinical use		X				XX					X								
Identify, address barriers to genomic medicine implementation		X	X	X			X	X	X										
Promote interaction and collaboration, reduce duplication	X		X	X		X	X	X		X		X			X	X		X	
Serve as clearinghouse, knowledge base for genomic medicine						XX		X			X								
Use genomics to enable new drug development														X	X				
Create genomics-enabled learning health care systems			X	X	X										X				
Develop evidence base for clinical use of novel diagnostics														X					
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	AFMS	CMG	CPIC	GA4GH	GAPH	GTEx	IOM	ISCC	LSAC	PAGE	PhenX

Barriers to genomic medicine implementation as identified by focus and related programs; "XX" indicates critical barrier.

Barriers Identified	Focus Programs								Related Programs												
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEx	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN
DATA/INFORMATION NEEDS																					
Evidence base for implement'n incl long-term outcomes			X	X			X	X						X							
Common data elements	X					X						X		X					X		
Development, validation of phenotypes			X	X															X		
Specific drug response phenotypes to add to trials																					X
Publicly available genotype/phenotype info						X			X			X									
Framework for classifying/curating actionable variants			X			X															
Unclear penetrance of actionable genes			X	X		X															
Frequency, impact of variants in ancestrally diverse pop'ns			X	X		X												X			
Loss of interoperability btwn sequence data repositories													X								
RAPIDLY EVOLVING NATURE OF GENOMIC INFO																					
Evolving molecular testing panels					X																
Changes in evidence and subsequent treatment		X	X		XX																
Division between discovery and implementation																	X				
CLINICAL IMPLEMENTATION ISSUES																					
High cost of sequencing, data processing								X									X				
Targeted testing vs genome-scale sequencing			X																		
Limited use of standardized EMR terms, ontologies				X		X															
Concise, comprehensive, interoperable lab reports			X							X											
Integration of genomic data in learning healthcare system			X	X																	
Turnaround in clinically emergent settings			X																		
Use cases for genomic CDS development										X											
Limited usefulness and interoperability of CDS				X	X		X	X													
Rapidly evolving EMRs					XX																
Limited transportability of clinical workflows, protocols			X		XX																
Differing education needs across professional levels					X																
Returning incidental findings				X									X								
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNe	PhenX	PGRN

Barriers Identified	Focus Programs								Related Programs												
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN
REGULATORY NEEDS																					
Central IRB	X																				
Sharing identifiable data across collaborating sites	X					X															
Privacy threats (FISMA compliance for UDN)	X			X																	
Regulations impeding return of results	X	XX	X																		
Need for cloud computing																X		X			
Reimbursement policies and regulations	XX		X																		
OTHER																					
Lack of centralized iPS cell repository												X									
Installing and using sequence analysis software													X								
Different tools for variant calling give different results													X								
Finding and interpreting CNVs and SVs													X								
Difficulty focusing on specific genes in massive BAMs													X								
Need secure systems enabling access by many users						X										X					
Harnessing social media and crowdsourcing methods						X													X		
Increasing visibility and use of tools; tracking uptake						X													X		
Need for bedside back to bench research				X			X														
Publication standards for rapid research results						X			X												
Worldwide ascertainment of Mendelian families									X												
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN