Integrating Genomic Sequencing into Clinical Care: CSER and Beyond

September 28, 2015

Workshop Report

Executive Summary

On September 28, 2015, the National Human Genome Research Institute (NHGRI) convened a workshop to discuss scientific questions and opportunities that can substantively be addressed by a future program in clinical sequencing. Participants proposed the following recommendations for NHGRI's consideration in each of six topic areas they were asked to address.

Facilitating Development of a Shared Evidence Base for Healthcare Systems

- Recognizing the need for an extensive and integrated knowledge base, develop, implement and disseminate site-specific models for learning healthcare systems that capture phenotype and health outcomes. Such systems should incorporate data both within and outside of NHGRI clinical sequencing activities
- Building upon experience to refine clinical tools, guidelines and recommendations based in part on CSER data and experience (e.g., ACMG recommendations), continue to facilitate the development of recommendations/guidelines for clinical sequencing in disease-specific and general genetics organizations
- Include families of individuals undergoing genomic testing in future studies
- Continue to generate evidence to inform regulatory and policy decision-making related to genetic medicine

Interpreting Variants / Actionability

- Improve standards for consistency, accuracy, and turnaround time in variant classification, including what evidence must be used for annotation, re-phenotyping, and re-interpreting data
- Generate and share additional data, to pre-emptively address gaps in evidence used to create guidelines and refine existing guidelines as they are used in the community
- Broaden and deepen the evidence base used for variant interpretation by:
  - Aggregating case-level data across multiple sites and contributing to case-level resources tailored to clinical data
  - Improving integration of databases and resources to synthesize and analyze heterogeneous data sources, facilitating accrual of evidence needed to assess clinical validity and clinical utility
  - Linking genotype data to family and longitudinal phenotype data to assess penetrance
- Assess and further enhance interactions between laboratories and clinicians to improve quality of clinical interpretation
- Link to other practitioner educational efforts related to variant interpretation and annotation

Assessing Clinical Utility

- Define specific measures of utility for clinical sequencing and improve how they are measured
- Adopt multiple approaches to studying and improving clinical utility, such as randomized designs and comparative effectiveness approaches , including comparison of clinical sequencing with other approaches in clinical medicine; establish how to harmonize or consider multiple measures at once
- Integrate rephenotyping data based on conditions known or suspected to be associated with a given genetic variant, to potentially improve diagnosis
- Deepen evaluation of long term health outcomes, including morbidity/mortality and aggregate measures
- Improve sequencing of structural variants and integration of functional genomic data to help capture a greater proportion of clinically meaningful variation
- As clinical sequencing becomes more prevalent in individuals without apparent disease, study its implications for population screening
- Assess the clinical utility of certain situations, such as diagnostic odyssey and reproductive decision making, that do not meet the traditional definition of "medical necessity", but are still widely considered reasons for genetic testing

Patient-centered Research: From Consent to Outcomes

- Conduct studies incorporating patient-centered and family-centered perspectives, including:
  - The value of making a diagnosis as a patient-centered outcome
  - The impact of diagnosis on subsequent outcomes
  - Potential differences in the meaning of "actionability" to patients/family vs. physicians/payers
  - Near-term patient-specific outcomes of pharmacogenomic and diagnostic findings
- Leverage resources to connect patients with researchers and foster community, including the development of alternative approaches for Internet-wary patients
- Develop approaches and platforms to incorporate patient preferences in receiving genomic results, particularly variants of unknown significance
- Be flexible in adopting patient-centered approaches that can change as technology changes and the number and diversity of populations increases

Increasing Ancestral, Socioeconomic and Clinical Diversity

- Maximize the equitable distribution of gains in genomic medicine
- Design studies with diversity in mind, consistent with scientific goals
- Implement targeted methodologies and approaches
  - Focus on trust, work with community-based institutions
  - Recruit and sustain participation by underrepresented individuals
  - Be sensitive to barriers to participation (loss of income, transportation costs, etc.)
- Study the social determinants of health in conjunction with genomic and clinical information
- Broaden all aspects of diversity, including workforce diversity

Healthcare Utilization, Economics and Value

- Study the cascading effects of receiving genomic results on subsequent healthcare utilization by individuals and their family members as well as potential interventions to reduce unnecessary utilization
- Engage payers and providers on education and study design in the assessment process in order to evaluate the value of genomic tests in current as well as future models of reimbursement
- Develop and study methods to assess the impact of clinical sequencing on better patient care, health care quality, and delivery as well as potential variation in the quality of genomic medicine in conjunction with clinical sequencing and methods for better health care delivery
- Generate evidence to address legal, regulatory and policy issues in reimbursement that will influence the dissemination of genomic applications
- Utilize common measures and pool data as feasible

Main Report

Ushered in by the completion of the human genome sequence, coupled with advances in technology development, genomically informed diagnosis and treatment, and computational efficiency, the era of clinical sequencing is upon us. The evidence base for the use of genomic sequence to diagnose and treat patients in a clinical setting has evolved rapidly over the past several years. When the National Human Genome Research Institute (NHGRI) established the Clinical Sequencing Exploratory Research (CSER) Program in 2011 (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-017.html), the opportunity to comprehensively and routinely consider the application and utilization of genomic sequence data in clinical care was nascent and ripe for research to address critical questions about the application of genomic sequencing to clinical care of individual patients. There were unanswered questions as to which clinical contexts would be best served using a genomic sequencing approach, how analysis and interpretation tools should be standardized, and what bottlenecks existed in developing the infrastructure needed for clinical sequencing. A broad examination of the ethical and psychosocial implications of generating, interpreting and returning genomic sequencing results to physicians and patients in a clinical setting was also needed. Now in 2015, per-genome sequencing costs have decreased over 10-fold since CSER's inception in 2011 (www.genome.gov/sequencingcosts) and resources are available for standardized interpretations of genetic variants [1]. As a result, clinical sequencing in many contexts has become increasingly cost- and time-efficient. However, the value of genomic information to an individual's health and healthcare goes beyond costs, and must ultimately be addressed within a complex healthcare system. A key challenge to navigating this complex system is informed decision-making based on an evolving knowledge base that also considers clinical and personal utility, as well as access to needed genomic testing, potential impact on health disparities, and impact on follow-up resources.

To take stock of its existing efforts in clinical sequencing and anticipate future opportunities, NHGRI convened a workshop on *Integrating Genomic Sequencing into Clinical Care: CSER and Beyond* on September 28th, 2015. The objectives of the meeting were to: 1) summarize and evaluate key scientific contributions of the Clinical Sequencing Exploratory Research (CSER) Program; 2) identify and prioritize scientific opportunities and questions for the next 5-10 years that would address informed integration of genomic sequencing into clinical care; and 3) identify optimal organizational features of a potential follow-up program. The purpose of this report is to synthesize key discussion points and priority recommendations from the workshop. Feedback has been aggregated across session topics and speakers; for those interested in the full discussion, the meeting agenda and archived presentations are available at http://www.genome.gov/27562330. A background document describing CSER's accomplishments is available at http://www.genome.gov/Pages/Research/ResearchFunding/DGM/CSER/CSER_Background_Document.pdf.

Setting the context: current NHGRI and NIH efforts related to clinical sequencing
Speakers: Eric Green, Teri Manolio, Carolyn Hutter, Katrina Goddard, and Lucia Hindorff

Pursuant to its 2011 Strategic Plan, *Charting a Course for Genomic Medicine from Base Pairs to Benchside* [2], NHGRI has an active and evolving portfolio in genomic medicine. Envisioned as a "test drive" program in which research challenges and opportunities could be identified and pursued in an exploratory setting, CSER was initially born from the intersection of the Genome Sequencing Program (http://www.genome.gov/10001691), Division of Genomic Medicine (DGM; http://www.genome.gov/27550079) and NHGRI Strategic Plan "Science of Medicine" domain. It joins a number of other genomic medicine programs housed in DGM with complementary emphases on electronic health records (EHR), undiagnosed diseases, newborn sequencing, implementation of established genomic tests, and curation of clinically relevant variants. CSER initially included six sites with an interdisciplinary tripartite structure comprising a clinical study (Project 1), generation and interpretation of sequence data (Project 2) and ethical, legal and social implications (Project 3). This structure encouraged multidisciplinary interactions as well as a dedicated focus on the intersections and interactions among these Projects (e.g., health provider-patient, physician-lab). Within 18 months, three additional tripartite project sites and a Coordinating Center were funded and two ongoing related efforts were integrated: 1)—a consortium of investigator-initiated grants focused on ELSI issues (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-11-003.html, http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-11-004.html,); and, 2) the NHGRI Intramural ClinSeq study (http://www.genome.gov/20519355).

Encompassing a range of diverse clinical settings, including pediatric, cancer, cardiac, and healthy individuals, CSER has sequenced nearly 5000 individuals to date, and has contributed to the evidence base describing analytical and clinical validity and clinical utility of exome and genome sequencing. Through site-specific advances as well as CSER-wide Working Groups, CSER has refined criteria for the evaluation of genomic variants for pathogenicity, estimated the yield of diagnostic and secondary findings in recruited patients, proposed approaches to defining the incremental benefit of genomic sequencing, conducted healthcare utilization studies, and suggested recommendations or best practices for display of genetic information in the EHR, informed consent, and disclosure of genomic results. Opportunities and recommendations for future work in these and related areas have also been described at related workshops, including recommendations on Clinical Sequencing from the NHGRI Future Opportunities for Sequencing and Beyond meeting [3] and the NHGRI Genomic Medicine 8 meeting [4]. Looking ahead to the next 5-10 years, several high priority areas have now been identified: clinical diagnosis of unsolved cases; determination of appropriate use of gene panels, exome and genome sequencing; increased emphasis on patient-centered outcomes and larger, more diverse populations; evaluation of downstream health and economic outcomes; optimization of the delivery system; and iterative phenotyping.

Developing a shared evidence base for healthcare systems
Moderators: Dan Roden, Ian Krantz. Speakers: Heidi Rehm, Dan Masys

As genomic research on human health and disease moves from basic to translational, the extent to which clinical research occurs in the context of the larger healthcare ecosystem becomes more apparent. Within CSER, sharing variant-level interpretations among clinical laboratories, returning diagnostic and secondary genomic results to patients, and developing robust interactions between patients and health providers are examples of clinical research activities occurring within this ecosystem, with implications for patients, laboratories, and practitioners. Engaging the clinical community traditionally occurs via practice-based clinical guidelines, and evidence from CSER has contributed to the development and subsequent refinement of American College of Medical Genetics and Genomics (ACMG) guidelines on secondary findings [5] and pathogenicity criteria [6]. The value-added of genomic medicine research also includes the opportunity and responsibility to engage stakeholders such as payers and non-genetics healthcare professionals who will influence the adoption of genomic sequencing in routine clinical care. Further, gaps exist between recommendations and physician behavior, and data on when and why clinicians do not follow recommendations would be useful. One vision for moving beyond clinical guidelines, which are static, includes a healthcare system which learns from every encounter. A subsequent clinical sequencing program could facilitate the development of a shared evidence base by developing, implementing and disseminating site-specific models for learning healthcare systems. These model systems could be regarded as extensions of existing data sharing models, in which sites continue to use existing infrastructure to integrate clinical sequencing data with phenotype data, as is done currently in CSER through dbGaP and ClinVar. Models might extend to include health outcomes and health utilization data and dissemination through case-level (i.e., at the level of the individual patient) resources that are more tailored to clinical data. Such model systems would also rely on developing local protocols and governance structures for broad data sharing. Complementing other efforts, a future clinical sequencing program could encourage physicians and laboratories to collect phenotypes in a standardized format conducive to EHR integration as research participants are recruited and followed up. Ideally, more effort would be taken to catalog downstream patient implications and clinical actions to build a systems-level infrastructure to capture information across sites (e.g., a genomic decision support library). Such a resource should attempt to capture all downstream clinical information and not simply focus on rare clinical events such as adverse drug reactions. Future NHGRI clinical sequencing programs should also leverage existing experience with patient-physician-laboratory interactions and include components related to family engagement, phenotyping and return of results. Ultimately, the shared evidence base should also produce evidence that can be used for legal, regulatory, and policy decision-making, learn from non-NHGRI funded sequencing efforts, and provide a seamless connection between research and clinical care.

Variant interpretation and actionability
Moderators: Debra Leonard, Levi Garraway. Speakers: Gail Jarvik, Elaine Lyon.

Recent progress has been made by the scientific community in annotating and interpreting genetic variants for clinical relevance. The use of *a priori* gene lists for considering secondary results for

return by laboratories was formalized by ACMG in 2013 [5]. Professional guidelines regarding annotation of pathogenicity were also recently issued [6], facilitating the standardization of variant interpretation. The diversity of approaches and clinical contexts within CSER facilitates empirical approaches to developing and refining recommendations such as these. For example, site-specific practices related to reporting of both primary and secondary findings vary within the CSER consortium, accommodating genes of particular diagnostic relevance to each site's disease focus or reflecting professional judgment regarding additional genes relevant to secondary findings. Sites have summarized approaches to identifying actionable genes, shared data with ClinVar and disseminated site-specific gene lists. Additionally, a series of variant interpretation "bakeoffs" using lab- and ACMG-specific pathogenicity criteria are providing an opportunity to assess consistency of variant classification using standardized criteria, and are shedding light on areas that need further attention (e.g., interpretation of low penetrance variants and consistent interpretation of functional studies). As these recommendations were being developed, CSER sites shared relevant resources with the professional society committees, pre-emptively addressing gaps in evidence used to create the recommendations. Experience gained through use of the recommendations post -development is also helping to identify and address potential gaps in existing recommendations and the evidence supporting them.

In the next 5-10 years, continued work will be needed to broaden the evidence base used for variant interpretation in relation to clinical decision-making and to make these activities more accessible to clinical laboratories, practitioners, and policymakers. A more complete and reliable understanding of the clinical and phenotypic implications associated with specific variants requires interaction between sequencing laboratories and practitioners, including the sharing of variant interpretations, phenotypes and other relevant case-level data through resources such as ClinVar, that are tailored to clinical data. Use of this information more broadly requires improvements to existing databases/resources, including the potential to link a patient's entire interpreted genome or exome to the EHR, to reanalyze data as the knowledge base evolves, and to iteratively phenotype patients. All of these recommendations underscore the link between genomic variants and clinical phenotype and the process by which variant interpretation, and re-interpretation, will only improve as knowledge accrues and as the interactions between labs and practitioners deepen. Notably, the notion of uncertain significance of variants is inherent to the dynamic nature of this process and participants saw parallels to other fields of medicine, such as radiology. Even with improved standards, knowledge and data sharing, there will still be levels of uncertainty and areas of disagreement. General efforts to familiarize practitioners, including non-genetics practitioners, with the nuances of variant interpretation, will be needed to appropriately counsel patients and their families.

Assessing Clinical Utility
Moderators: Mary Relling, Arul Chinnaiyan. Speakers: Robert Green, Euan Ashley.

The diagnostic yield of exome or genome sequencing is a common metric used to evaluate clinical utility. Interpretation of this metric becomes more complicated as one considers sequencing in individuals without overt clinical phenotypes and as the implications of sequencing broaden to clinically relevant secondary findings or changes in diagnosis. Clinical yields of pathogenic or likely pathogenic variants across various clinical contexts (presence or absence of disease, response to treatment, age)

have been measured across CSER sites and should continue to be measured in a future clinical sequencing program. In some clinical contexts, e.g., tumor sequencing, evidence shows that the depth of coverage and cost- and time- efficiency of gene-based panels currently outweighs the benefits of exome or genome sequencing. For pharmacogenes, terms other than "pathogenic" are needed to describe functional consequences of variants. The integration of broad and deep phenotype information, with diagnostic and secondary genomic findings, is also needed to assess penetrance. In the future, metrics will need to be refined as it becomes clearer which genomic tests are most appropriate in different clinical contexts.

Several recommendations related to methodological approaches were suggested for future studies. Participants emphasized the need for comparative effectiveness research and traditional methodologies such as randomized controlled trials to determine the incremental value of exome or genome sequencing over alternate approaches, including non-genomic based approaches. Randomized controlled trials are being incorporated in some of the existing CSER sites; however, these trials have relatively small sample sizes. As clinical sequencing becomes more prevalent and sample sizes for analysis increase, methods optimized for either common disease or N = 1 studies may need to be adapted as case-level data are aggregated for genotype-phenotype analysis. Capturing all clinically relevant variation will require incorporating alternate sequencing modalities that interrogate clinically relevant variation that is missed with current next-generation sequencing technologies (e.g, structural variation). As above, research protocols for rephenotyping are needed, as will effective and efficient methods for integrating functional genomic studies with clinical sequencing findings.

As clinical utility data become part of the evidence base necessary for clinical implementation, NHGRI should carefully consider how to foster the "virtuous cycle" of research and clinical care. Clarification of what constitutes useful metrics and to what extent such metrics encompass individual, family or societal benefit is also needed. Some measures of utility are less amenable to precise definition, such as the value of simply making a diagnosis, or of having information that is not necessarily clinically actionable. As clinical sequencing methods are continually improved and as experience accrues from clinical practice, so metrics will continue to evolve over time. Finally, as clinical sequencing is performed more frequently in apparently healthy individuals, the implications for population screening (for example, the potential benefits as well all downstream risks and costs) should also be studied.

Patient-centered Research: From Consent to Outcomes
Moderators: Chanita Hughes Halbert, Ben Wilfond. Speakers: Steve Joffe, Matt Might.

The notion of patient-centered research is integral to many of the existing components of CSER that address ethical, legal, and psychosocial implications of clinical sequencing, which have spanned from studying the informed consent process to studying preferences regarding the return of results and reactions to receiving results. Through peer-reviewed publications, CSER has shared conceptual models, genetic counseling cases, and best practices regarding consent forms. These publications highlight common themes and challenges that have been addressed across the sites, such as facilitating

participant understanding and informed decision-making, as well as the need for diversity in approaches based on such factors as disease context and participant age. Investigators have also studied patients' preferences for receiving secondary results, as well as clinician and system challenges. Defining and measuring common patient-centered outcomes within CSER is in progress as well.

Receiving a diagnosis is a key patient-centered moment, particularly for patients and families who have undergone a "diagnostic odyssey," and current genomic medicine research places a heavy value on diagnosis. Participants strongly encouraged extending ongoing work to encompass familial and economic implications of receiving diagnostic or secondary genomic results. Follow-up of the patient and family should extend beyond the diagnosis to better understand its impact, including subsequent outcomes as well as outcomes that may have occurred in the absence of a diagnosis. Recognizing that patient advocacy and citizen scientist groups now have increasing convening power around recruitment and data analysis, NHGRI should leverage resources to connect patients/family members sharing common genetic or phenotypic information with researchers. Flexibility in such approaches will be needed as technology evolves, and to include a diversity of populations. Another area of future research with a dedicated patient focus is how, and not simply what, results should be returned. Relative to practitioners, patients may prefer more accessible (e.g., mobile-based) or customizable formats and may have a broader notion of what information, including variants of unknown significance, may be meaningful or actionable. Indeed, even the possibility of convening other patients with shared genomic or phenotypic information may be viewed by some patients as a next action, contributing to the idea that to a patient in search of an answer, "everything is actionable." Pursuing these patient-centered models within a broader health system requires addressing governance of the data as well as aspects of data sharing that will address concerns at the individual/family level as well as the system level.

Increasing Ancestral, Socioeconomic and Clinical Diversity
Moderators: Pilar Ossorio, Greg Cooper. Speakers: James Evans, Carlos Bustamante.

That CSER and related genomic medicine programs occur in a broader societal context was particularly evident as participants considered the ways in which CSER should broaden ancestral, socioeconomic and clinical diversity (referred to henceforth simply as "diversity"). As one example of a CSER site recruiting diverse individuals, the University of North Carolina, Chapel Hill observed that the participation rate for minority participants was dependent heavily on practical issues and is enhanced through trust, coordination with healthcare, and geographical proximity. As CSER and related efforts continue to build an evidence base for clinical sequencing, it is imperative to ensure that any resulting advances in genomic medicine are equitably distributed. To date, there has not been sufficient inclusion of diverse populations, and NHGRI should implement deliberate and targeted approaches to increasing diversity. First, diversity should be an integral feature of study design that will improve the quality of the science, for example, through comprehensiveness of sampling and integrated approach to studying genetic and socioeconomic health determinants. In some cases, groups with particular relevance for the scientific questions at hand may need to be oversampled to achieve maximal scientific benefit and address health disparities. Efforts should be made to include populations that are traditionally not

considered to be underrepresented, but that may be underrepresented in clinical sequencing studies, or who have a high burden of a particular disease. Even with the proper questions and sampling design in hand, however, much work must be done to recruit and sustain participation from diverse populations. A common theme from CSER and external investigators was to focus on building trust in communities. Different models are likely to work; however, the end goals should encompass not just increased enrollment but empowerment of individuals, both patients/families and practitioners, to take action. It is also important to recognize substantial barriers to participation in some populations, such as loss of income due to time away from work and lack of basic healthcare for following up abnormal research findings, particularly those with lower socio-economic status. A final recommendation was to broaden workforce diversity.

Healthcare Utilization, Economics and Value

Moderators: Katrina Armstrong, Sharon Plon. Speakers: David Veenstra, Pat Deverka.

Envisioning a health system in which genomic information is part of the standard of care requires engaging diverse stakeholders to maximize the relevance of genomics to different healthcare systems. A diagnostic or secondary genomic result can potentially end a complicated diagnostic odyssey, change the course of treatment, or begin a cascade of follow-up for an individual and potentially, for his/her family members. The implications of these different outcomes are incompletely understood and future efforts should integrate measures of healthcare utilization, economics and value. CSER has published work on health economics and cost-effectiveness, and is currently harmonizing measures of healthcare utilization across sites. In a future clinical sequencing program, work done by CSER could be extended in a number of key areas. Comparative effectiveness studies of multiple genetic testing modalities could be enabled, to facilitate identification of the best test for a given purpose. Data collection should extend to the identification of common cross-site measures and pooling of data where feasible. As noted above, the implications for family members are incompletely understood and yet will undoubtedly have impact on healthcare utilization and value.

Future clinical sequencing research should address issues relevant to regulatory decision making and reimbursement, recognizing that policy in both of these areas is evolving. Researchers as well as payers are still learning what evidence is needed, so a framework within which relative priorities are outlined, rather than one that focuses simply on whether or not tests are covered, may be more appropriate. Recognizing that payers currently work within a strict contractual model for determining pre-authorization or reimbursement, a model of phased or provisional implementation may be more feasible in the near term as evidence is accumulating. New models of reimbursement, such as bundled payments and accountable care, where health organizations partner with payers in a coordinated way, should be considered when evaluating the value of genomic applications. Methods for involving payers in study conception and design should be considered; a payer advisory board might be one model. With regard to regulation of genomic testing, NHGRI recognizes the need to interact with regulatory agencies and when possible, contribute data and evidence to inform these agencies.

Summary and conclusions

Moderators: Robert Nussbaum, Lucilla Ohno-Machado. Summary: Lucia Hindorff, Carolyn Hutter.

Participants affirmed that CSER has made substantial progress in building the evidence base for clinical sequencing in diverse settings, as demonstrated by implementing sequencing pipelines in clinical settings; becoming aware of and sharing lessons learned in interpretation and return of genomic results; assessing clinical utility in a diagnostic and broader clinical context; sharing best practices for consent and results disclosure, and assessing patient-centered outcomes. The synergy among the CSER sites in these areas has led to the whole of CSER being much more than the sum of its parts. CSER fills a unique position in studying the patient-practitioner interaction and should continue its focus on characterizing the clinical encounter. As NHGRI considers future opportunities for its clinical sequencing portfolio, there was consensus on several high priority recommendations, organized below into broad conceptual areas and guiding principles.

Conceptual areas:

- Demonstrating the clinical utility of genomic sequencing through appropriately designed studies, in collaboration with stakeholders, and with recognition that the healthcare system is a resource-constrained setting
- Incorporating genomic modalities in addition to exome or genome sequencing, such as gene panels, where appropriate, to better understand the value added of exome or genome sequencing beyond targeted panels
- Characterizing the personal, economic and clinical impact of a patient's genomic results on subsequent healthcare utilization and implications for family members (the "cascade")
- Addressing the growing gap between decreasing costs of sequencing and increasing costs of interpretation and return of results, with a focus on making interpretation and return of results more efficient and accessible
- Improving standards for consistency in variant classification, including evidence used for annotation, re-phenotyping, and re-interpreting data. Data sharing with case-level resources tailored toward clinical data should be encouraged as feasible, to pre-emptively address gaps in evidence used to create the guidelines and refine gaps in released guidelines as they are used in the community.

Guiding principles

- Diversifying the ancestral and socioeconomic background of patients and practitioners
- Retaining a broad scientific framework similar to that of CSER. Although the instantiation of a rapid learning health system requires concerted efforts beyond the purview of NHGRI alone, in the spirit of fostering such a system, any future clinical sequencing program should retain a broad framework similar to that of CSER, encompassing patient, practitioner and laboratory components, and integrating ELSI. Within this broad framework, scientific questions to be addressed should be specified *a priori*, with particular attention to the interactions among

patients, practitioners, and laboratories that will generate the evidence needed for the above areas.

- Continuing to pursue ELSI components of CSER. It was clear that the ELSI components of CSER, initially designated as required and deliberately integrated, should continue to be pursued, and both an integrated ELSI component and an independent ("non-embedded") ELSI component should be maintained.
- Retaining a consortium emphasis in high priority scientific areas. The value of a consortium approach was evident through activities such as the variant interpretation bake-off, which demonstrated benefit to individual sites as well as the CSER consortium, and will refine and improve future guidelines issued by professional societies.
- Preserve nimbleness to take advantage of unanticipated opportunities, as was done in CSER with respect to interacting with professional societies as recommendations were developed, or to address unexpected constraints.

The initial exploratory approach to CSER has begun to generate the evidence and next set of scientific questions necessary for the appropriate implementation of genomic sequencing into clinical care. For a future clinical sequencing program, continuing to frame these questions around the interactions of patients, practitioners and laboratories will further understanding of how to achieve personalized healthcare at the individual level and improve the effectiveness of healthcare.

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Appendix 2. Meeting agenda.

National Human Genome Research Institute

Integrating Genomic Sequencing into Clinical Care: CSER and Beyond

DoubleTree by Hilton Hotel
Bethesda, MD

September 28, 2015

MEETING OBJECTIVES:

1. To summarize and evaluate key scientific contributions of the Clinical Sequencing Exploratory Research (CSER) Program.
2. To identify and prioritize scientific opportunities and questions for the next 5-10 years that would address informed integration of genomic sequencing into clinical care.
3. To identify optimal organizational features of a potential follow-up program.

Opening Remarks

8:15-8:30am	Call to order and introductions	Lucia Hindorff
8:30-8:50am	Setting the Context *15 min. presentation, 5 min. Q&A.*	Eric Green
8:50-9:05am	NHGRI's Genomic Medicine Portfolio *10 min. presentation, 5 min. Q&A.*	Teri Manolio
9:05-9:15am	Recommendations from NHGRI's 2014 Workshop: Future Opportunities for Genome Sequencing & Beyond	Carolyn Hutter
9:15-9:40am	CSER: Veni, Vidi, and a Roadmap to Vici *20 min. presentation, 5 min. Q&A*	Katrina Goddard
9:40-9:50am	NHGRI Perspective on CSER and Overview of Meeting Topics	Lucia Hindorff

Presentations and Discussion

All topics below include consideration of relevant ELSI issues

9:50-10:40am	Facilitating Development of a Shared Evidence Base for Healthcare Systems	Moderators: Dan Roden, Ian Krantz Challenges/ opportunities: Heidi Rehm (10 min.) Reaction: Dan Masys (10 min.) Group Discussion: 25 min. Summary: Dan Roden (5 min.)
10:40-11:00am	*Break*	
11:00-11:50am	Interpreting Variants / Actionability	Moderators: Debra Leonard, Levi Garraway Challenges/ opportunities: Gail Jarvik (10 min.) Reaction: Elaine Lyon (10 min.) Group Discussion: 25 min. Summary: Debra Leonard (5 min.)
11:50am-12:40pm	Assessing Clinical Utility	Moderators: Mary Relling, Arul Chinnaiyan Challenges/ opportunities: Robert Green (10 min.) Reaction: Euan Ashley (10 min.) Group Discussion: 25 min. Summary: Mary Relling (5 min.)
12:40-1:10pm	Working lunch (pick up lunches)	
1:10-2:00pm	Patient-centered Research: From Consent to Outcomes	Moderators: Chanita Hughes Halbert, Ben Wilfond Challenges/ opportunities: Steve Joffe (10 min.) Reaction: Matt Might (10 min.) Group Discussion: 25 min. Summary: Chanita Hughes Halbert (5 min.)

2:00-2:50pm	Increasing Ancestral, Socioeconomic and Clinical Diversity	Moderators: Pilar Ossorio, Greg Cooper Challenges/ opportunities: Jim Evans (10 min.) Reaction: Carlos Bustamante (10 min.) Group Discussion: 25 min. Summary: Pilar Ossorio (5 min.)
2:50-3:40pm	Healthcare Utilization, Economics and Value	Moderators: Katrina Armstrong, Sharon Plon Challenges/ opportunities: Dave Veenstra (10 min.) Reaction: Pat Deverka (10 min.) Group Discussion: 25 min. Summary: Katrina Armstrong (5 min.)
3:40-4:00pm	*Break*	
4:00-5:30pm	Meeting Summary and Prioritizing Future Opportunities in the Next 5-10 years *15 minutes for summary slides, 75 minutes moderated discussion*	Summary slides: Lucia Hindorff and Carolyn Hutter Moderators: Bob Nussbaum and Lucila Ohno-Machado
5:30-5:45pm	Closing comments	Eric Green
5:45pm	Adjourn	

Appendix 3. Acknowledgments

- National Advisory Council for Human Genome Research (http://www.genome.gov/10000905) and the following Working Groups:
    - Genomic Medicine Working Group (http://www.genome.gov/27549220)
    - Genomics and Society Working Group (http://www.genome.gov/27551917)
- Sequencing Advisory Panel: William Gelbhardt, chair; Ewan Birney, Rex Chisholm, Andy Clark, Rod McInnes, Deirdre Meldrum, Len Pennacchio, Pamela Sankar, Alan Williamson
- CSER Advisory Panel: Katrina Armstrong, chair; Rex Chisholm, Mildred Cho, Chanita Hughes Halbert, Elaine Lyon, Ken Offit, Dan Roden, Pamela Sankar, Alan Williamson
- NHGRI leadership: Eric Green, Teri Manolio, Jeff Schloss, Larry Brody, Bettie Graham, Rudy Pozzatti
- *CSER and Beyond* meeting planning
    - Planning Committee: Chanita Hughes Halbert, Debra Leonard, Mary Relling, Dan Roden
    - Logistics: Saundra Bromberg, Capital Consulting
    - Workshop preparation and report: Lucia Hindorff, Carolyn Hutter, Dave Kaufman, Alex Lee, Teri Manolio, Jean McEwen, Elian Silverman