The Clinical Sequencing Evidence-Generating Research Consortium: Integrating Genomic Sequencing in Diverse and Medically Underserved Populations

Laura M. Amendola,[1] Jonathan S. Berg,[2] Carol R. Horowitz,[3,4] Frank Angelo,[1] Jeannette T. Bensen,[5] Barbara B. Biesecker,[6] Leslie G. Biesecker,[7] Gregory M. Cooper,[8] Kelly East,[8] Kelly Filipski,[9] Stephanie M. Fullerton,[10] Bruce D. Gelb,[11] Katrina A.B. Goddard,[12] Benyam Hailu,[13] Ragan Hart,[1] Kristen Hassmiller-Lich,[14] Galen Joseph,[15] Eimear E. Kenny,[16] Barbara A. Koenig,[17] Sara Knight,[18] Pui-Yan Kwok,[19] Katie L. Lewis,[7] Amy L. McGuire,[20] Mary E. Norton,[21] Jeffrey Ou,[1] Donald W. Parsons,[22] Bradford C. Powell,[2] Neil Risch,[19] Mimsie Robinson,[23] Christine Rini,[24] Sarah Scollon,[25] Anne M. Slavotinek,[26] David L. Veenstra,[27] Melissa P. Wasserstein,[28] Benjamin S. Wilfond,[29] Lucia A. Hindorff,[30] on behalf of the CSER consortium, Sharon E. Plon,[25] and Gail P. Jarvik[1,31,*]

The Clinical Sequencing Evidence-Generating Research (CSER) consortium, now in its second funding cycle, is investigating the effectiveness of integrating genomic (exome or genome) sequencing into the clinical care of diverse and medically underserved individuals in a variety of healthcare settings and disease states. The consortium comprises a coordinating center, six funded extramural clinical projects, and an ongoing National Human Genome Research Institute (NHGRI) intramural project. Collectively, these projects aim to enroll and sequence over 6,100 participants in four years. At least 60% of participants will be of non-European ancestry or from underserved settings, with the goal of diversifying the populations that are providing an evidence base for genomic medicine. Five of the six clinical projects are enrolling pediatric patients with various phenotypes. One of these five projects is also enrolling couples whose fetus has a structural anomaly, and the sixth project is enrolling adults at risk for hereditary cancer. The ongoing NHGRI intramural project has enrolled primarily healthy adults. Goals of the consortium include assessing the clinical utility of genomic sequencing, exploring medical follow up and cascade testing of relatives, and evaluating patient-provider-laboratory level interactions that influence the use of this technology. The findings from the CSER consortium will offer patients, healthcare systems, and policymakers a clearer understanding of the opportunities and challenges of providing genomic medicine in diverse populations and settings, and contribute evidence toward developing best practices for the delivery of clinically useful and cost-effective genomic sequencing in diverse healthcare settings.

Background

As the cost of genomic sequencing tests has decreased, researchers have increasingly explored the practical and ethical considerations of implementing these technologies clinically. Several groups have reported the diagnostic rate from genomic sequencing tests, including the National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI)-funded Clinical Sequencing Exploratory Research consortium (CSER-phase one). Diagnostic rates in

[1]Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA 98195, USA; [2]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [3]Center for Health Equity and Community Engaged Research, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [4]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [5]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [6]Research Triangle Institute, International, Washington DC 20005, USA; [7]Medical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA; [8]HudsonAlpha Institute for Biotechnology, Huntsville, AL 35806, USA; [9]National Cancer Institute, National Institutes of Health, Bethesda, MD 20850, USA; [10]Department of Bioethics and Humanities, University of Washington, Seattle, WA 98195, USA; [11]Departments of Pediatrics and Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [12]Center for Health Research, Kaiser Permanente Northwest, Portland, OR 97227, USA; [13]National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD 20892, USA; [14]Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [15]Department of Anthropology, History & Social Medicine, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94143, USA; [16]Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [17]Program in Bioethics, Institute for Health and Aging, University of California-San Francisco, San Francisco, CA 94118, USA; [18]Division of Preventive Medicine, University of Alabama at Birmingham, and Birmingham VA Medical Center, Birmingham, AL 35294, USA; [19]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA 94143, USA; [20]Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, TX 77030, USA; [21]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, CA 94143, USA; [22]Texas Children's Cancer Center and Department of Pediatrics, Baylor College of Medicine, Houston, TX, 77030, USA; [23]Bethel Gospel Assembly, New York, NY 10035, USA; [24]Department of Biomedical Research, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ 07601, USA; [25]Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA; [26]Department of Pediatrics, Division of Genetics, University of California, San Francisco, San Francisco, CA 94158, USA; [27]Department of Pharmacy, University of Washington, Seattle, WA 98195, USA; [28]Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY 10467, USA; [29]Department of Pediatrics and Seattle Children's Research Institute, University of Washington, Seattle, WA 98195, USA; [30]Division of Genomic Medicine, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA; [31]Department of Genome Sciences, University of Washington, Seattle, WA 98195, USA
*Correspondence: gjarvik@medicine.washington.edu
https://doi.org/10.1016/j.ajhg.2018.08.007.

CSER-phase one were reported for participants with cancer (6% for pathogenic and likely pathogenic variants), cardiomyopathy (27%), and intellectual disability (28%).[1] A relatively high diagnostic yield (60%) in individuals with retinal dystrophies, as well as other Mendelian or neurological disorders, has also been reported.[2,3] The rate of medically actionable secondary findings identified by genomic sequencing ranges from 1% to 3% of cases,[4,5] depending on the population evaluated, genes annotated, and criteria used in variant interpretation. Hence, genomic sequencing can be a useful diagnostic test, especially for certain phenotypes, and can identify previously unknown actionable genetic conditions providing the opportunity for targeted interventions that may improve health outcomes.

Projects in CSER-phase one, as well as others, have identified key ethical and practical considerations for informed consent and return of results that are raised by genomic sequencing. Most adult patients and parents of pediatric patients express interest in learning their results from these tests,[6–8] although this interest varies across individuals, clinical settings and by type of finding.[9,10] Interest in genetic results can also be influenced by the severity of one's illness and psychological factors such as knowledge of benefits, worry about genetic risks, anticipated regret for learning or not learning the findings, and health information seeking style.[11] The scope and potential uncertainty of results have been identified as essential to discuss during informed consent conversations;[12] and it is critical to develop informed consent processes and documentation that can be understood by a diverse population.[13,14] Similarly, it is critical to manage hopes and expectations, and triage the return of large amounts of information when returning results from genomic sequencing.[15–20] Finally, CSER-phase one projects examined difficulties and approaches to navigating the separation between clinical care and research while conducting consent and return of results conversations in the context of clinical genomics research.[21]

Challenges with managing the results from genomic sequencing tests have also been examined, especially for primary care or specialist providers who have limited training and experience in clinical genetics.[22,23] Educational programs exist for non-genetics health professionals and have been shown to be beneficial in enhancing knowledge, self-efficacy, and confidence, among other outcomes.[24] Yet, these educational programs might not significantly change practice.[25]

Patients and researchers face obstacles to the implementation of genomic medicine. Barriers to participation in genomic research studies include lack of community engagement, mistrust on the part of the patient, logistical barriers, and privacy and discrimination concerns.[31,32] These barriers are likely exacerbated in underserved populations. Additional challenges for genomic medicine implementation research in underserved groups include a lack of diversity in the scientific community, smaller sample sizes, and the analytical challenges faced when studying participants of mixed ancestry.[33] Access to clinical genomic sequencing is also limited by workforce capacity and distribution, reimbursement models, regulation requirements, and lack of evidence-based guidance on clinical utility.[34,35]

International efforts to address genomic medicine implementation include the United Kingdom's Genomics England project, which plans to sequence the genomes of 100,000 patients with rare diseases, the families of these patients, and patients with cancer. Australia's Melbourne Genomics Health Alliance is assessing and establishing systems to incorporate genomic sequencing in select disease areas, and Canada's Genomics and Personalized Health competition (GAPH) includes 17 separate large-scale genomics research projects informing evidence-based and cost-effective health care.[36]

Despite all that has been learned, most early efforts have inadequately addressed diverse or underserved populations, and the field lacks sufficient evidence to inform the effective application of genomic technologies in these populations and clinical settings.[26] Improving the evidence base for genomic testing, gaining data to interpret variants of uncertain significance, making gains in reimbursement, enhancing collaborative interpretation, and data sharing have all been reported as unsolved challenges for genomic medicine.[27,28] Additionally, most studies have focused on participants who are of European ancestry and are relatively well-educated, insured, and financially secure.[29] Optimal genomic implementation practices are likely to vary across patients from different social, economic and cultural backgrounds. As such, genomic research conducted in diverse populations and healthcare settings should enhance the broad application of genomic medicine.[30] In 2017, the United States NHGRI, NCI, and National Institute on Minority Health and Health Disparities (NIMHD) funded the current phase of the CSER consortium, a network of projects studying the integration of genomic sequencing into clinical care. The consortium is emphasizing engagement of patients from non-European populations, underserved populations, or populations known to experience poorer medical outcomes. Each project within the consortium plans to enroll a minimum of 60% of participants with these characteristics, targeting recruitment in a range of healthcare settings beyond academic medical centers to advance the effective use of clinical genomics more broadly. The CSER consortium RFA defined underserved populations based on the definition of "medically underserved" provided by the Health Resources and Services Administration, which identifies geographic areas and populations with a lack of access to primary care services (see Web Resources). Discussions to modify this definition to increase consistency across CSER consortium clinical project populations are underway.

The objectives of the research program are to: (1) define, generate, and

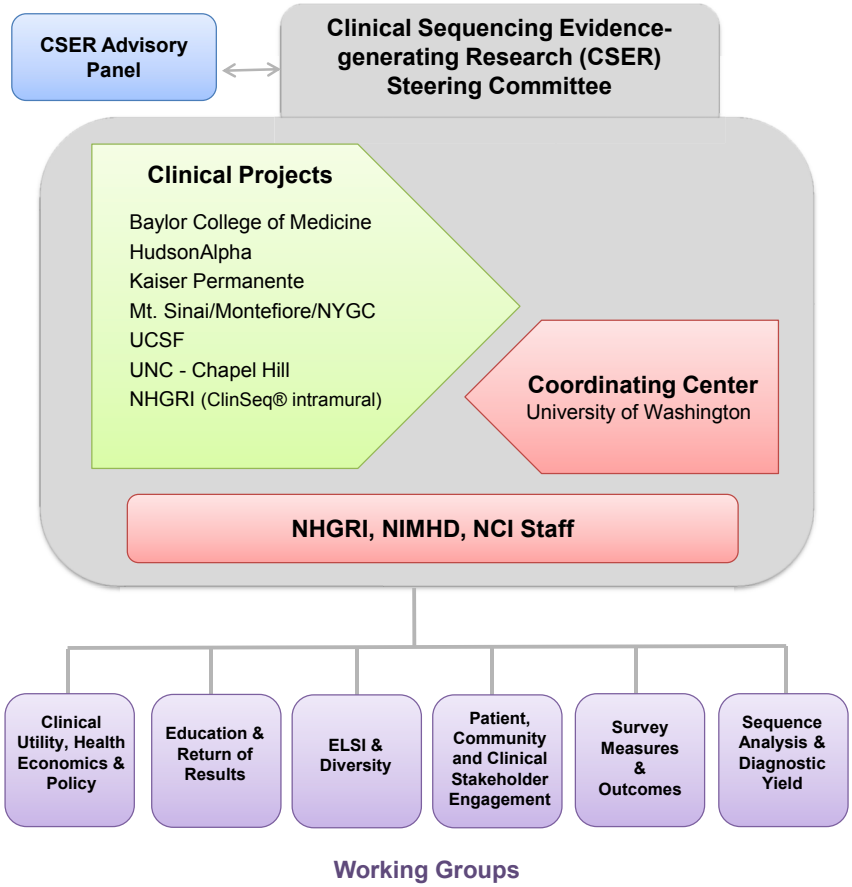

Figure 1. Structure of the CSER Consortium
The components of the CSER consortium and their relationships to each other.

analyze data regarding the clinical utility of genome sequencing; (2) study the critical interactions among patients, family members, health practitioners, and clinical laboratories that influence implementation and outcomes of clinical genomic sequencing; and (3) identify and address real-world barriers to integrating genomic, clinical, and healthcare utilization data within multiple U.S. healthcare systems to build a shared evidence base for clinical decision-making (See Web Resources section). Relevant ethical, legal, and social issues (ELSI) are also a major feature of the consortium, and research of this type is integrated across the aims of each funded project. Building on the prior work of CSER-phase one, the CSER consortium is now positioned to expand upon the evidence needed for effective genomic sequencing implementation in diverse settings.

Clinical Projects

The CSER consortium comprises six extramural clinical projects, an NHGRI intramural project (ClinSeq), and a centralized coordinating center (Figure 1). Five of the six extramural clinical projects are enrolling children with phenotypes including neurodevelopmental, neurological, immunological, and cardiac disorders, as well as pediatric cancer diagnoses. One of these five projects is also enrolling parents whose fetus has a structural anomaly. The sixth clinical project is enrolling adults with a focus on hereditary cancer risk. The estimated cohort size for each of these six projects ranges from 850 to 1,500 participants, and proposed enrollment of racially diverse participants ranges from 45% to 85% across sites. Racially diverse participants are defined as those who identify as Hispanic/Latino, Black/African American, American Indian/Alaska Native, Asian, and/or Native Hawaiian/Pacific Islander. A specific category to track enrollment of Southeast Asian participants has also been added. In addition, ClinSeq has enrolled a population of 500 adults who self-identify as African, African American, or Afro-Caribbean and are unselected for phenotype.

Genomic sequencing technology varies across the projects, including germline exome and genome sequencing and targeted panels, as well as pediatric tumor exome and transcriptome sequencing. The projects also vary in terms of who is disclosing results (both genetics and non-genetics providers) and how they are disclosed (via mail, telemedicine with visualization, web portals, telephone, and in person). All projects plan to return pathogenic and/or likely pathogenic variants in secondary finding genes. Secondary findings will include all or a subset of conditions recommended for return by the American College of Medical Genetics and Genomics (ACMG),[37] and some sites have added additional genes to this list. Some projects are also returning pathogenic variants for select autosomal recessive disorders (carrier status). Each project is working with clinical populations at multiple locations ranging from outpatient clinics and community hospitals to large academic medical centers and the intensive care units within these tertiary care centers. Thus, these projects will assess many different aspects of genomic medicine. Additional information about each study population and protocol are presented in Table 1.

Consortium Organization

The CSER consortium structure includes six working groups and a Steering Committee (Figure 1), which oversees the high-level goals and direction of the consortium. The CSER consortium Advisory Panel comprises six investigators and a community advocate, with expertise in pediatrics, cancer, healthcare utilization, clinical laboratory technologies and standards, engagement of diverse populations,

Table 1. CSER Consortium Projects and Key Information about Their Study Populations and Protocols

Contact Institution	Project	Population	Targeted Diversity Groups	Care sites	Technology	Results Disclosure	Key Outcomes
Baylor College of Medicine	KidsCanSeq	Children with cancer	Medically underserved, Hispanic, African American	Academic and non-academic medical centers, outpatient clinics	Germline ES, tumor ES and transcriptome versus targeted panel testing	Negative results by mail; telemedicine versus in person for positive results	Clinical utility; Perceived utility; Family member testing
ClinSeq	ClinSeq A2	Adults, no specific phenotype	African American, Afro- Caribbean, African	National Institutes of Health Clinical Center	Germline ES	Web portal versus GC for negative secondary findings	Understanding; Risk perception
Kaiser Permanente Northwest	CHARM	Adults at risk for hereditary cancer	Minority, low SES, Medicaid/Medicare or uninsured, Spanish speaking	Outpatient clinics	Germline ES versus usual care	Literacy-focused versus traditional GC by phone	Understanding of recommended actions/ care; Adherence to recommended care; Personal utility
The University of North Carolina, at Chapel Hill	NCGENES 2	Children with suspected genetic conditions (developmental disabilities, dysmorphology, neuromuscular disorders)	African American, Hispanic, Medicaid or uninsured	Outpatient pediatric genetic and neurology clinics at academic medical centers; community hospital	Germline ES versus usual care	In-person or telemedicine by genetics and non-genetics providers	Benefit of pre-visit educational materials on patient and provider encounters; Clinical utility
Icahn School of Medicine at Mount Sinai	NYCKidSeq	Children with suspected neurologic, immunologic and cardiac genetic conditions	African American, Hispanic, Medicaid/ Medicare, Spanish speaking	Academic medical center	Germline GS versus targeted panel	In-person counseling standard of care versus communication tool enhanced	Understanding and satisfaction; Clinical utility; Economic utility
University of California, San Francisco	P^3EGS	Infants and children with severe developmental disorders, with or without congenital anomalies; parents whose fetus has a structural anomaly	Underserved by census tract/ MediCal status, Asian, Hispanic, African American	Academic medical center, outpatient clinics, neonatal intensive care unit, and pediatric intensive care unit; Community hospital, outpatient clinic	Germline ES, duos or trios	In person or telemedicine	Clinical utility; Understanding of recommended actions/ care; Adherence to recommended care; Personal utility
Hudson Alpha Research Institute	South-Seq	Newborns with suspected genetic conditions	African American, underserved rural	Academic and non-academic medical centers	Germline GS	Genetics and non-genetics providers	Empower non- genetics providers to return genetics results; Scalability to rural and community medical centers

GS, genome sequencing; ES, exome sequencing; SES, socioeconomic status; GC, genetic counseling.

Table 2. Focus and Harmonization Plans for CSER Working Groups

Group	Focus	Current cross-consortium harmonization plans
Clinical Utility, Health Economics, and Policy	- Developing framework to define clinical utility - Meetings with payers and policymakers - Standardizing assessment of framework constructs - Cross-consortium analyses informed by common measures	- Cost and completion of genomic testing and return of genomic test results - Provider perceived benefits of genomic testing and recommended actions attributable to testing - Adherence to recommended actions post return of results - Impact of genomic testing on health status
SI and Diversity	- Challenges in diverse populations - Impact of racial, ethnic and socioeconomic diversity on access to and delivery of genomic medicine and health care - Enrollment-related measures (consent, enrollment barriers, etc.) - Disparities in genomic medicine and research, and public health - Issues related to emerging health IT innovations	- Race/ethnicity/ancestry - Other categories of difference: zip code, patient activation, trustworthiness - Model consent language for consortium data sharing
Education and Return of Results	- Educating both patients and providers - Optimizing return of results for diverse patient populations - Patient satisfaction with return of results method - Implications of diagnostic and secondary findings; family-related factors and clinical decision support	- Participant satisfaction - Family communication - Utilization of information sources - Genomic sequencing report design - Negative result disclosure
Survey Measures and Outcomes	- Patients' and family members' knowledge, attitudes, beliefs, behaviors and psychological outcomes - Provider knowledge, attitudes, beliefs and behaviors, including diagnostic thinking and management planning - Assessing health system leaders' buy in	- Demographics and socioeconomic status - Rationale for decline and withdrawal - Provider confidence, perceived utility - Participant uncertainty, positive/negative emotions, privacy concerns, health literacy, personal utility, understanding - Health system readiness to change
Patient, Community, and Clinical Stakeholder Engagement	- Addressing common practices and challenges, and evaluating levels and types of engagement across sites - Assessing quality and impact of engagement - Involvement of patients and community advocates	- Support for short and long-term needs across sites - Process evaluation of quality and impact of engagement
Sequence Analysis and Diagnostic Yield	- Harmonizing/understanding differences in definitions of diagnostic rate to enable cross-consortium comparisons - Laboratory-provider interactions - Sharing data and technical improvements - Diverse population representation in genomic databases - Impact of variant reinterpretation on yield and cost	- Classification of case-level results for diagnostic and secondary findings - Reporting of secondary findings - Use of ancestral data inferred from genetic sequence - Phenotypic descriptions - Indications for testing

genetic counseling, and ELSI. Representatives from the NHGRI, NCI, and NIHMD participate on the Steering Committee and are also involved with each CSER working group. The development of the working groups began with a review of the CSER-phase one groups and was further informed by consideration of existing critical issues in genomic medicine by the clinical site principal investigators, the coordinating center and NHGRI leadership. Through this process, the six working groups were formed: ELSI and Diversity; Stakeholder Engagement; Clinical Utility, Health Economics, and Policy; Education and Return of Results, Survey Measures and Outcomes; and Sequence Analysis and Diagnostic Yield.

Each working group deliberated and selected common domains to be harmonized across projects to facilitate the optimal integration of data. These efforts are focused on a shared, evolving conceptual framework that identifies which domains fall within the scope of each working group so they can develop related hypotheses. For example, the Clinical Utility, Health Economics, and Policy working group, which is focused on healthcare utilization, has proposed a standardized approach for each site to measure adherence to recommendations after the return of genomic sequencing results, and the Education and Return of Results working group has developed a harmonized measure to evaluate satisfaction with the different modes of result return across the CSER consortium projects. The focus of each working group and the consortium-wide projects being pursued by each group are presented in Table 2.

Harmonized measures across the consortium are available on the CSER consortium public website (see Web Resources section).

High-Priority Areas of CSER Consortium Investigation

Delivering Genomic Medicine in Non-Academic Institutions

Under the right circumstances, the uptake of genetic services can be high. This may be especially true for germline cancer susceptibility testing, even when offered in a low resource, safety-net clinic[38] where there is often less genetics expertise among clinicians, and patients are diverse in socioeconomic status, ancestry, language, and education. Although knowledge of genetic testing is increasing in diverse communities,[39] social and cultural context can be expected to influence the success of genetic services.[40,41] As outlined, the care sites of CSER consortium projects include outpatient clinics and community hospitals. Some research has investigated germline cancer sequencing in diverse populations;[42–44] however, newer genetic testing options, such as exome and genome sequencing for pediatric disorders, have not been well studied in these clinical settings. The CSER consortium offers the opportunity to further investigate and generate evidence to improve genomic medicine implementation beyond the setting of specialized genetic medicine clinics in academic centers. Additionally, both providers and patients in these non-academic settings are likely to benefit from the availability of genomic medicine resources.

Stakeholder Engagement

In order to work effectively with diverse populations, researchers and members of various stakeholder groups need to establish a trusting relationship.[45] Relevant stakeholders can also contribute to the development of research ideas, strategies for study conduct and ways to use results to inform health policy.[46] Thus, the CSER consortium has made stakeholder engagement a high priority. Previous work by the NHGRI Electronic Medical Records and Genomics (eMERGE) Network has highlighted key stakeholder practices, challenges, and considerations in the context of projects focused on incorporating genomic information into electronic health records.[47] Findings highlight the need to engage stakeholder groups beyond patients (e.g., organizational leadership), use clear communication and consistent language across groups, especially with underserved populations and non-English speakers, and conduct engagement activities (e.g., surveys, interviews, group meetings, etc.) throughout all phases of implementation. CSER consortium projects are seeking input from a variety of stakeholders in the early planning stages of their projects so they can inform study design and the development of recruitment and consent materials. Key stakeholder groups identified for engagement include patients and parents of pediatric patients, clinicians, community members, patient advocates, health system leadership and payers. Several projects have also established advisory committees to provide consultation throughout their study, including feedback about communication of results, understanding of healthcare recommendations, educational and support needs, and best practices for disseminating findings to the community.

Engagement of Non-English-Speaking Patients

The quality of communication between patients and their care providers is an important factor that influences healthcare outcomes.[48] Nearly half of the United States adult population has limited health literacy, and nearly 1 in 10 Americans having limited English proficiency.[49] Delivering genetic services to patients in the United States who are not English speaking has been little studied, though some research has shown that being a non-English speaker is associated with lower understanding of results and recommendations,[50,51] knowledge of genetic disease,[52] and uptake of genetic testing.[52] Appropriate non-English terms to support return of genomic results are needed.[53] Many CSER consortium projects expect to enroll substantial numbers of non-English-speaking participants and are developing materials in Spanish and hiring bilingual and multilingual study personnel to support recruitment, informed consent and return of results for improved communication with these participants. Non-English speaking individuals will also be members of project advisory boards and play a key role in stakeholder engagement activities. Conducting genomic medicine implementation research with non-English speaking patients will enable the CSER consortium to inform best practice recommendations that are applicable to patients with diverse cultural backgrounds.

Participant Perception of Personal Utility

Patients tend to have a broader conceptualization of utility than medical actionability; for example, including results that inform changes in medical care, reproductive planning, and future life planning generally.[54] The personal utility of genomic sequencing encompasses the non-clinical benefits that arise from this technology. Participant-perceived personal benefits can include satisfying curiosity, increasing self-knowledge and awareness, gaining in-depth knowledge and understanding of one's condition, and justifying re-evaluating life priorities.[55,56] Patients from different social, economic, and cultural backgrounds might have different expectations about the potential benefits of these tests.[57] The CSER consortium projects plan to explore measuring participant perceptions of personal utility across their diverse study populations to further refine the definition of this concept, highlight the broad impacts of genomic medicine and understand contextual factors that influence utility perceptions, such as clinical setting, purpose of sequencing, and access to health professionals.

Moving Forward

As the clinical projects within the CSER consortium gain experience implementing their protocols, the consortium will continue to explore cross-site collaborations through

additional data sharing. The CSER consortium is also part of a larger network of NHGRI consortia, including the eMERGE network, the Implementing Genomics in Practice (IGNITE) consortium, and the Clinical Genome (ClinGen) Resource. These cross-consortia relationships, as well as interactions with the All of US national precision medicine program and others, foster partnerships and increase learning opportunities with each consortium contributing its unique perspective to projects on shared topics of interest. Members of the CSER consortium will continue to contribute to the development of evidence-based recommendations for the implementation of genomic sequencing in diverse clinical care settings, addressing current challenges and new questions that arise through the work of the consortium.

Acknowledgments

This work was funded by ZIA HG200387, U01 HG006485, U01 HG007301, U01 HG007292, U01 HG006487, U01 HG009610, U01 HG009599, and U24 HG007307. L.G.B. and K.L.L. were supported by the intramural research program of the National Human Genome Research Institute, grant HG200359 09. The authors thank Melpi Kasapi and Ellen Howerton for logistical support, as well as Kevin Bowling, Tia Kauffman, and Nuriye Sahin-Hodoglugil for their contributions.

Declaration of Interests

M.E.N. has research support from Natera and is a consultant and on the Scientific Advisory Board for Invitae. L.G.B. is an uncompensated advisor to the Illumina Corporation and received royalties from Genentech Inc. S.E.P. is on the Scientific Advisory Board of Baylor Genetics. All other authors declare no relevant conflicts of interest.

Web Resources

CSER, https://cser-consortium.org/

HRSA Health Workforce,https://bhw.hrsa.gov/shortage-designation/muap

Department of Health and Human Services, https://grants.nih.gov/grants/guide/rfa-files/RFA-HG-16-011.html

References

1. Green, R.C., Goddard, K.A.B., Jarvik, G.P., Amendola, L.M., Appelbaum, P.S., Berg, J.S., Bernhardt, B.A., Biesecker, L.G., Biswas, S., Blout, C.L., et al.; CSER Consortium (2016). Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine. Am. J. Hum. Genet. *98*, 1051–1066.
2. Yavarna, T., Al-Dewik, N., Al-Mureikhi, M., Ali, R., Al-Mesaifri, F., Mahmoud, L., Shahbeck, N., Lakhani, S., AlMulla, M., Nawaz, Z., et al. (2015). High diagnostic yield of clinical exome sequencing in Middle Eastern patients with Mendelian disorders. Hum. Genet. *134*, 967–980.
3. Lee, K., Berg, J.S., Milko, L., Crooks, K., Lu, M., Bizon, C., Owen, P., Wilhelmsen, K.C., Weck, K.E., Evans, J.P., and Garg, S. (2015). High Diagnostic Yield of Whole Exome Sequencing in Participants With Retinal Dystrophies in a Clinical Ophthalmology Setting. Am. J. Ophthalmol. *160*, 354–363.e9.
4. Yang, Y., Muzny, D.M., Xia, F., Niu, Z., Person, R., Ding, Y., Ward, P., Braxton, A., Wang, M., Buhay, C., et al. (2014). Molecular findings among patients referred for clinical whole-exome sequencing. JAMA *312*, 1870–1879.
5. Amendola, L.M., Dorschner, M.O., Robertson, P.D., Salama, J.S., Hart, R., Shirts, B.H., Murray, M.L., Tokita, M.J., Gallego, C.J., Kim, D.S., et al. (2015). Actionable exomic incidental findings in 6503 participants: challenges of variant classification. Genome Res. *25*, 305–315.
6. Jamal, L., Robinson, J.O., Christensen, K.D., Blumenthal-Barby, J., Slashinski, M.J., Perry, D.L., Vassy, J.L., Wycliff, J., Green, R.C., and McGuire, A.L. (2017). When bins blur: Patient perspectives on categories of results from clinical whole genome sequencing. AJOB Empir. Bioeth. *8*, 82–88.
7. Regier, D.A., Peacock, S.J., Pataky, R., van der Hoek, K., Jarvik, G.P., Hoch, J., and Veenstra, D. (2015). Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete-choice experiment. CMAJ *187*, E190–197.
8. Hitch, K., Joseph, G., Guiltinan, J., Kianmahd, J., Youngblom, J., and Blanco, A. (2014). Lynch syndrome patients' views of and preferences for return of results following whole exome sequencing. J. Genet. Couns. *23*, 539–551.
9. Bennette, C.S., Trinidad, S.B., Fullerton, S.M., Patrick, D., Amendola, L., Burke, W., Hisama, F.M., Jarvik, G.P., Regier, D.A., and Veenstra, D.L. (2013). Return of incidental findings in genomic medicine: measuring what patients value–development of an instrument to measure preferences for information from next-generation testing (IMPRINT). Genetics in medicine: official journal of the American College of Medical Genetics *15*, 873–881.
10. Lewis, M.A., Stine, A., Paquin, R.S., Mansfield, C., Wood, D., Rini, C., Roche, M.I., Powell, C.M., Berg, J.S., and Bailey, D.B. Jr. (2018). Parental preferences toward genomic sequencing for non-medically actionable conditions in children: a discrete-choice experiment. Genetics in medicine: official journal of the American College of Medical Genetics *20*, 181–189.
11. Rini, C., Khan, C.M., Moore, E., Roche, M.I., Evans, J.P., Berg, J.S., Powell, B.C., Corbie-Smith, G., Foreman, A.K.M., Griesemer, I., et al. (2017). The who, what, and why of research participants' intentions to request a broad range of secondary findings in a diagnostic genomic sequencing study. Genetics in Medicine *20*, –769.
12. Bernhardt, B.A., Roche, M.I., Perry, D.L., Scollon, S.R., Tomlinson, A.N., and Skinner, D. (2015). Experiences with obtaining informed consent for genomic sequencing. Am. J. Med. Genet. A. *167A*, 2635–2646.
13. Niemiec, E., Vears, D.F., Borry, P., and Howard, H.C. (2018). Readability of informed consent forms for whole-exome and whole-genome sequencing. J. Community Genet. *9*, 143–151.
14. Fowler, S.A., Saunders, C.J., and Hoffman, M.A. (2018). Variation among Consent Forms for Clinical Whole Exome Sequencing. J. Genet. Couns. *27*, 104–114.
15. Amendola, L.M., Lautenbach, D., Scollon, S., Bernhardt, B., Biswas, S., East, K., Everett, J., Gilmore, M.J., Himes, P., Raymond, V.M., et al.; CSER Genetic Counseling Working Group (2015). Illustrative case studies in the return of exome and genome sequencing results. Per. Med. *12*, 283–295.
16. Khan, C.M., Moore, E.G., Leos, C., and Rini, C. (2016). Patient hopes for

diagnostic genomic sequencing: roles of uncertainty and social status. Eur. J. Hum. Genet. *24*, 803–808.
17. Kaphingst, K.A., Ivanovich, J., Lyons, S., Biesecker, B., Dresser, R., Elrick, A., Matsen, C., and Goodman, M. (2018). Preferences for learning different types of genome sequencing results among young breast cancer patients: Role of psychological and clinical factors. Transl. Behav. Med. *8*, 71–79.
18. Christensen, K.D., Bernhardt, B.A., Jarvik, G.P., Hindorff, L.A., Ou, J., Biswas, S., Powell, B.C., Grundmeier, R.W., Machini, K., Karavite, D.J., et al. (2018). Anticipated responses of early adopter genetic specialists and nongenetic specialists to unsolicited genomic secondary findings. Genetics in Medicine. Published February 1, 2018. https://doi.org/10.1038/gim.2017.243.
19. Wynn, J., Lewis, K., Amendola, L.M., Bernhardt, B.A., Biswas, S., Joshi, M., McMullen, C., and Scollon, S. (2018). Clinical providers' experiences with returning results from genomic sequencing: an interview study. BMC Med. Genomics *11*, 45.
20. Skinner, D., Roche, M.I., Weck, K.E., Raspberry, K.A., Foreman, A.K.M., Strande, N.T., Berg, J.S., Evans, J.P., and Henderson, G.E. (2018). "Possibly positive or certainly uncertain?": participants' responses to uncertain diagnostic results from exome sequencing. Genetics in Medicine *20*, 313–319.
21. Wolf, S.M., Amendola, L.M., Berg, J.S., Chung, W.K., Clayton, E.W., Green, R.C., Harris-Wai, J., Henderson, G.E., Jarvik, G.P., Koenig, B.A., et al. (2018). Navigating the research-clinical interface in genomic medicine: analysis from the CSER Consortium. Genetics in Medicine *20*, 545–553.
22. Douma, K.F., Smets, E.M., and Allain, D.C. (2016). Non-genetic health professionals' attitude towards, knowledge of and skills in discussing and ordering genetic testing for hereditary cancer. Fam. Cancer *15*, 341–350.
23. Gray, S.W., Park, E.R., Najita, J., Martins, Y., Traeger, L., Bair, E., Gagne, J., Garber, J., Janne, P.A., Lindeman, N., et al. (2016). Oncologists' and cancer patients' views on whole-exome sequencing and incidental findings: results from the CanSeq study. Genetics in Medicine *18*, 1011–1019.
24. Talwar, D., Tseng, T.S., Foster, M., Xu, L., and Chen, L.S. (2017). Genetics/genomics education for nongenetic health professionals: a systematic literature review. Genetics in Medicine *19*, 725–732.
25. Paneque, M., Turchetti, D., Jackson, L., Lunt, P., Houwink, E., and Skirton, H. (2016). A systematic review of interventions to provide genetics education for primary care. BMC Fam. Pract. *17*, 89.
26. Hall, M.J., and Olopade, O.I. (2006). Disparities in genetic testing: thinking outside the BRCA box. J. Clin. Oncol. *24*, 2197–2203.
27. Bertier, G., Sénécal, K., Borry, P., and Vears, D.F. (2017). Unsolved challenges in pediatric whole-exome sequencing: A literature analysis. Crit. Rev. Clin. Lab. Sci. *54*, 134–142.
28. Bertier, G., Hétu, M., and Joly, Y. (2016). Unsolved challenges of clinical whole-exome sequencing: a systematic literature review of end-users' views. BMC Med. Genomics *9*, 52.
29. Popejoy, A.B., and Fullerton, S.M. (2016). Genomics is failing on diversity. Nature *538*, 161–164.
30. Hindorff, L.A., Bonham, V.L., Brody, L.C., Ginoza, M.E.C., Hutter, C.M., Manolio, T.A., and Green, E.D. (2018). Prioritizing diversity in human genomics research. Nat. Rev. Genet. *19*, 175–185.
31. Cohn, E.G., Husamudeen, M., Larson, E.L., and Williams, J.K. (2015). Increasing participation in genomic research and biobanking through community-based capacity building. J. Genet. Couns. *24*, 491–502.
32. Amendola, L.M., Robinson, J.O., Hart, R., Biswas, S., Lee, K., Bernhardt, B.A., East, K., Gilmore, M.J., Kauffman, T.L., Lewis, K.L., et al. (2018). Why Patients Decline Genomic Sequencing Studies: Experiences from the CSER Consortium. J. Genet. Couns. Published March 1, 2018. https://doi.org/10.1007/s10897-018-0243-7.
33. Bentley, A.R., Callier, S., and Rotimi, C.N. (2017). Diversity and inclusion in genomic research: why the uneven progress? J. Community Genet. *8*, 255–266.
34. Gaff, C.L., I, M.W., S, M.F., D, P.H., Clark, J., P, M.W., South, M., and A, H.S. (2017). Preparing for genomic medicine: a real world demonstration of health system change. NPJ genomic medicine *2*, 16.
35. Ginsburg, G.S. (2013). Realizing the opportunities of genomics in health care. JAMA *309*, 1463–1464.
36. Manolio, T.A., Abramowicz, M., Al-Mulla, F., Anderson, W., Balling, R., Berger, A.C., Bleyl, S., Chakravarti, A., Chantratita, W., Chisholm, R.L., et al. (2015). Global implementation of genomic medicine: We are not alone. Sci. Transl. Med. *7*, 290ps13.
37. Kalia, S.S., Adelman, K., Bale, S.J., Chung, W.K., Eng, C., Evans, J.P., Herman, G.E., Hufnagel, S.B., Klein, T.E., Korf, B.R., et al. (2017). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genetics in medicine *19*, 249–255.
38. Komenaka, I.K., Nodora, J.N., Madlensky, L., Winton, L.M., Heberer, M.A., Schwab, R.B., Weitzel, J.N., and Martinez, M.E. (2016). Participation of low-income women in genetic cancer risk assessment and BRCA 1/2 testing: the experience of a safety-net institution. J. Community Genet. *7*, 177–183.
39. Vadaparampil, S.T., Wideroff, L., Breen, N., and Trapido, E. (2006). The impact of acculturation on awareness of genetic testing for increased cancer risk among Hispanics in the year 2000 National Health Interview Survey. Cancer Epidemiol. Biomarkers Prev. *15*, 618–623.
40. Lagos, V.I., Perez, M.A., Ricker, C.N., Blazer, K.R., Santiago, N.M., Feldman, N., Viveros, L., and Weitzel, J.N. (2008). Social-cognitive aspects of underserved Latinas preparing to undergo genetic cancer risk assessment for hereditary breast and ovarian cancer. Psychooncology *17*, 774–782.
41. Ricker, C.N., Koff, R.B., Qu, C., Culver, J., Sturgeon, D., Kingham, K.E., Lowstuter, K., Chun, N.M., Rowe-Teeter, C., Lebensohn, A., et al. (2018). Patient communication of cancer genetic test results in a diverse population. Transl. Behav. Med. *8*, 85–94.
42. Nanda, R., Schumm, L.P., Cummings, S., Fackenthal, J.D., Sveen, L., Ademuyiwa, F., Cobleigh, M., Esserman, L., Lindor, N.M., Neuhausen, S.L., and Olopade, O.I. (2005). Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. JAMA *294*, 1925–1933.
43. Armstrong, K., Micco, E., Carney, A., Stopfer, J., and Putt, M. (2005). Racial differences in the use of BRCA1/2 testing among women with a family

history of breast or ovarian cancer. JAMA *293*, 1729–1736.
44. Guindalini, R.S., Win, A.K., Gulden, C., Lindor, N.M., Newcomb, P.A., Haile, R.W., Raymond, V., Stoffel, E., Hall, M., Llor, X., et al. (2015). Mutation spectrum and risk of colorectal cancer in African American families with Lynch syndrome. Gastroenterology *149*, 1446–1453.
45. Staunton, C., Tindana, P., Hendricks, M., and Moodley, K. (2018). Rules of engagement: perspectives on stakeholder engagement for genomic biobanking research in South Africa. BMC Med. Ethics *19*, 13.
46. Kaplan, B., Caddle-Steele, C., Chisholm, G., Esmond, W.A., Ferryman, K., Gertner, M., Goytia, C., Hauser, D., Richardson, L.D., Robinson, M., et al. (2017). A Culture of Understanding: Reflections and Suggestions from a Genomics Research Community Board. Progress in community health partnerships: research, education, and action *11*, 161–165.
47. Hartzler, A., McCarty, C.A., Rasmussen, L.V., Williams, M.S., Brilliant, M., Bowton, E.A., Clayton, E.W., Faucett, W.A., Ferryman, K., Field, J.R., et al. (2013). Stakeholder engagement: a key component of integrating genomic information into electronic health records. Genetics in Medicine *15*, 792–801.
48. Stewart, M.A. (1995). Effective physician-patient communication and health outcomes: a review. CMAJ *152*, 1423–1433.
49. Ryan, C. (2013). Language Use in the United States: 2011. American Community Survey Reports. US Department of Commerce, Economics and Statistics Administration (US CENSUS BUREAU).
50. Harrison, H.F., Harrison, B.W., Walker, A.P., Lohman, K., Ellis, S.D., Hall, M.A., Reiss, J., Adams, P.C., Holup, J., Acton, R.T., et al. (2008). Screening for hemochromatosis and iron overload: satisfaction with results notification and understanding of mailed results in unaffected participants of the HEIRS study. Genet. Test. *12*, 491–500.
51. Walker, A.P., Tucker, D.C., Hall, M.A., Lohman, K., Harrison, H., Harrison, B.W., Reiss, J., Acton, R.T., Adams, P.C., Diaz, S., et al. (2007). Results communication and patient education after screening for possible hemochromatosis and iron overload: experience from the HEIRS Study of a large ethnically and linguistically diverse group. Genetics in Medicine *9*, 778–791.
52. Suriadi, C., Jovanovska, M., and Quinlivan, J.A. (2004). Factors affecting mothers' knowledge of genetic screening. Aust. N. Z. J. Obstet. Gynaecol. *44*, 30–34.
53. Amanda, M., Gutierrez, J.O.R., Statham, Emily E., Scollon, Sarah, Bergstrom, Katie L., Slashinski, Melody J., Parsons, Donald W., Plon, Sharon E., McGuire, Amy L., and Street, Richard L. (2017). Portero versus portador: Spanish interpretation of genomic terminology during whole exome sequencing results disclosure. Per. Med. *14*, 503–514.
54. Yu, J.H., Crouch, J., Jamal, S.M., Bamshad, M.J., and Tabor, H.K. (2014). Attitudes of non-African American focus group participants toward return of results from exome and whole genome sequencing. Am. J. Med. Genet. A. *164A*, 2153–2160.
55. Kohler, J.N., Turbitt, E., Lewis, K.L., Wilfond, B.S., Jamal, L., Peay, H.L., Biesecker, L.G., and Biesecker, B.B. (2017). Defining personal utility in genomics: A Delphi study. Clin. Genet. *92*, 290–297.
56. Lewis, K.L., Hooker, G.W., Connors, P.D., Hyams, T.C., Wright, M.F., Caldwell, S., Biesecker, L.G., and Biesecker, B.B. (2016). Participant use and communication of findings from exome sequencing: a mixed-methods study. Genetics in Medicine *18*, 577–583.
57. Yu, J.H., Crouch, J., Jamal, S.M., Tabor, H.K., and Bamshad, M.J. (2013). Attitudes of African Americans toward return of results from exome and whole genome sequencing. Am. J. Med. Genet. A. *161A*, 1064–1072.