Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine

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Despite rapid technical progress and demonstrable effectiveness for some types of diagnosis and therapy, much remains to be learned about clinical genome and exome sequencing (CGES) and its role within the practice of medicine. The Clinical Sequencing Exploratory Research (CSER) consortium includes 18 extramural research projects, one National Human Genome Research Institute (NHGRI) intramural project, and a coordinating center funded by the NHGRI and National Cancer Institute. The consortium is exploring analytic and clinical validity and utility, as well as the ethical, legal, and social implications of sequencing via multidisciplinary approaches; it has thus far recruited 5,577 participants across a spectrum of symptomatic and healthy children and adults by utilizing both germline and cancer sequencing. The CSER consortium is analyzing data and creating publically available procedures and tools related to participant preferences and consent, variant classification, disclosure and management of primary and secondary findings, health outcomes, and integration with electronic health records. Future research directions will refine measures of clinical utility of CGES in both germline and somatic testing, evaluate the use of CGES for screening in healthy individuals, explore the penetrance of pathogenic variants through extensive phenotyping, reduce discordances in public databases of genes and variants, examine social and ethnic disparities in the provision of genomics services, explore regulatory issues, and estimate the value and downstream costs of sequencing. The CSER consortium has established a shared community of research sites by using diverse approaches to pursue the evidence-based development of best practices in genomic medicine.

Introduction

With the rapid advances in sequencing technology and variant interpretation, the era of genomic medicine by clinical genome and exome sequencing (CGES) is underway,[1–3] but there are substantial knowledge gaps in its application. In 2010 and 2012, the National Human Genome Research Institute (NHGRI) issued a request for applications (RFA) for a Clinical Sequencing Exploratory Research (CSER) program focused on identifying and

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generating evidence to address key challenges in applying sequencing to the clinical care of individuals.[4,5] These challenges span a range of issues surrounding the generation, analysis, and interpretation of CGES data, as well as the translation of these data for the referring physician, communication to the participant and families, and examination of the clinical utility and broader ethical, legal, and social implications (ELSIs) of utilizing genomic data in the clinic.

Grant applications in response to this RFA employed a three-project structure. Project 1 addressed "one or more areas of medical investigation (i.e., disease or therapeutic approach) or a specific approach to the use of genotype-phenotype data within a clinical context (e.g., risk prediction modeling or cancer mutation profiling)." Project 2 addressed "the development of methods to analyze genomic sequence data for clinically actionable variants, as well as parsing these data into manageable components to translate the findings into formats that eased interpretation of the findings by the clinician." Project 3 "investigated how patients understand, react to, and use individual genomic results when they are offered and returned … [and] investigate[d] the experiences of clinicians regarding the return of results." Nine sites were funded by the NIH cooperative agreement or U-award mechanism. In addition, the NHGRI intramural ClinSeq study joined the CSER consortium as a tenth site in 2013. These sites, including ClinSeq, are collectively described as the U-award sites for convenience throughout the rest of this paper.

In 2013, the CSER consortium was expanded to incorporate a pre-existing consortium (formerly known as the ELSI Return of Results Consortium) that included nine previously awarded projects relating to the return of research results and management of secondary findings (also called incidental findings) in both research and clinical settings. These projects (some initiated by investigators and some funded under RFAs)[6,7] used the NIH regular research grant or R-award mechanism and are collectively termed R-award sites in this paper. The consolidation of these projects under the CSER consortium umbrella has fostered intensive interactions among a diverse collection of clinicians, genomic researchers, social scientists, biomedical informaticians, bioethicists, and legal scholars. A CSER coordinating center[8] was funded in 2013 to facilitate collaborative efforts among the CSER investigators and to broadly disseminate information from the CSER consortium to the biomedical research community. Consortium investigators have collaborated to explore distinct but complementary approaches to utilizing CGES data in the practice of medicine. This report provides a high-level overview of the consortium, its accomplishments to date, and the community resources that have been generated. This report summarizes major steps that the CSER consortium has taken to improve the future of health care by beginning to develop clinical sequencing best practices and determining the effect of this technology on participants, providers, and the global health-care system. It also reviews steps that can be taken to further improve the clinical implementation of this developing technology and guide future health-care policies.

Overview of the CSER Consortium

The organization of the consortium and description of the sites are depicted in Figure 1 and Table 1. Four of the projects are focused solely on participants diagnosed with cancer or at an increased risk of cancer, whereas the remainder focus on participants with other medical conditions or self-reported healthy participants seen in primary care. Across the projects, there are adult and/or pediatric participant cohorts, and the centers provide exome and/or genome

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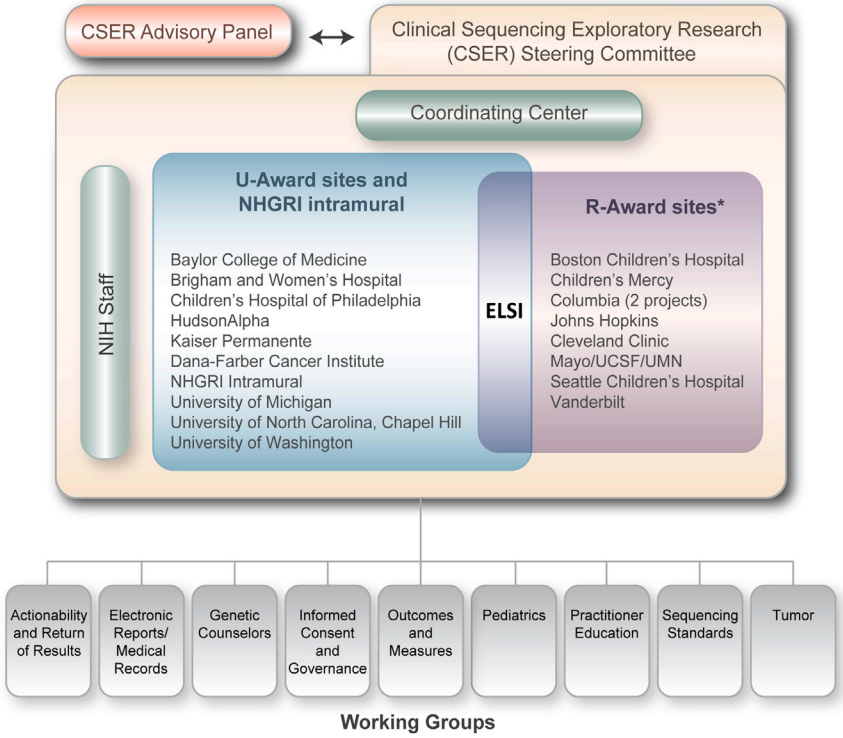

Figure 1. Schematic of the Structure of the CSER Consortium

Grants funded under RFA-HG-11-003 and RFA- HG-11-004 have ended, but the investigators on those grants continue to participate in consortium activities. Along with ELSI investigators on the U-awards, they meet regularly to discuss ELSI issues relevant to CSER. Note: this figure was updated for the purposes of this publication and is reproduced with permission from the CSER consortium; it is now available on the CSER website (see Web Resources).

sequencing (Table 1). The R-awards have considerable synergy with the ELSI components (project 3) of the U-award (Table 2). The ELSI projects utilize quantitative and qualitative empirical approaches, along with normative and legal analyses, in most cases by employing multiple methods. There are also nine cross-project, collaborative working groups (Table 3). Details of the U-award, the R-award, the consortium-wide working groups, and additional published and preliminary data are provided in the Supplemental Data.

As shown in Figure 2, the U-award sites collectively have thus far recruited 5,577 participants to date (4,429 adults and 1,148 children) and anticipate the eventual recruitment of approximately 7,101 participants, 6,210 of whom are subjects undergoing CGES, when enrollment at each of the sites is completed. Table 4 shows a further breakdown of the indications for sequencing and the diagnostic yields obtained.

Whereas each U-award project conforms to the tripartite requirements of the original RFA, the clinical studies include observational or interventional designs (including randomized trials). Some projects sequence only probands, whereas others sequence parent-child trios. In addition to performing exome and genome sequencing, one cancer project performs tumor RNA sequencing. Whereas some projects return results only from a list of known disease-associated genes, others return variants from any gene that has a potentially valid association. This variation in approach has resulted in differences among the studies in the diagnostic yield, defined as the percentage of participants with at least one plausible diagnostic genetic finding (Table 4). This variation also empowers creative analysis at the individual sites, enriches data available to the working groups, and provides opportunities to move toward increasingly evidence-based best practices for CGES. The goal of the various CSER working groups (Table 3) is to collaborate on common issues that arise in different ways across the sites to make collective recommendations. Many of the recommendations produced by these working groups will ultimately influence issues that will affect the clinical diagnostic yield of GCES. Although many of the individual studies have not yet completed their analyses, initial results from individual studies and cross-cutting collaborations are emerging, as highlighted below.

Sequencing Specifications and Variant Classification

Each U-award has developed and managed its own translational sequencing pipeline, including variant interpretation, that addresses the technical, analytic, and interpretive components of the clinical sequencing process.[2,26] The time between sample collection and the return of the interpreted report at the start of the CSER consortium projects was 16 weeks and is currently averaging about 13 weeks. Thus far, coverage of the sequenced target (exome or genome) has averaged 20× or greater over 89%–98% of the exome or genome. Average depth of coverage has ranged from 62× to 233× for germline exome sequencing, from 32× to 42× for germline genome sequencing, and from 166× to 250× for tumor exome sequencing. The Sequencing Standards working group is exploring the genome and exome coverage across the different platforms as defined by each site's pipeline to move toward a more comprehensive approach to clinical sequencing. All results being returned to participants are generated or confirmed in laboratories certified by the Clinical Laboratory Improvement Amendments (CLIA).

Table 1. CSER Consortium U-Awards

Project Name	Institutions[a]	Project Goal	Population	Tissue Type	Technique	Disease Status	Discloser of Results
BASIC3: Baylor Advancing Sequencing into Childhood Cancer Care	Baylor College of Medicine*	incorporating CLIA-certified tumor and blood exome sequencing	pediatric	germline and solid tumors	exome sequencing	known disease	oncologist with a genetic counselor present for consult if needed
CanSeq: The Use of Whole-Exome Sequencing to Guide the Care of Cancer Patients	Dana-Farber Cancer Institute,* Broad Institute of MIT and Harvard	improving cancer outcomes by identifying biologically consequential tumor alterations with existing or emerging technologies	adult	germline and solid tumors	exome sequencing	known disease	oncologist with a referral to genetic counseling if needed
ClinSeq: A Large-Scale Sequencing Clinical Research Pilot Study	National Human Genome Research Institute*	comparing identified genetic variants with individual and family-history information	adult	germline	exome sequencing	seemingly healthy	genetic counselor and/or medical geneticist
HudsonAlpha: Genomic Diagnosis for Children with Developmental Delay	HudsonAlpha Institute for Biotechnology,* University of Louisville	identifying genetic variations causing developmental delay, intellectual disability, and related phenotypes, as well as medically relevant secondary findings	adult and pediatric	germline	exome and genome sequencing	known disease	medical geneticist and genetic counselor
MedSeq: Integration of Whole Genome Sequencing into Clinical Medicine	Brigham and Women's Hospital,* Baylor College of Medicine, Broad Institute of MIT and Harvard, Duke University	integrating whole-genome sequencing into clinical medicine in healthy adults and adults with cardiomyopathy	adult	germline	genome sequencing	seemingly healthy and known disease	primary-care physician or cardiologist
MI-ONCOSEQ: Michigan Oncology Sequencing Center	University of Michigan,* Johns Hopkins University	implementing clinical sequencing for sarcomas and other rare cancers	adult and pediatric	germline and solid tumors	genome sequencing	known disease	oncologist with a referral to genetic counseling
NCGENES: North Carolina Clinical Genomic Evaluation by Next-Generation Exome Sequencing	University of North Carolina at Chapel Hill*	investigating the use of whole-exome sequencing in individuals with hereditary cancer susceptibility, genetic heart disorders, neurogenetic disorders, and congenital malformations	adult and pediatric	germline	exome sequencing	known disease	medical geneticist and genetic counselor
NEXT Medicine: Clinical Sequencing in Cancer: Clinical, Ethical, and Technological Studies	University of Washington*	studying the clinical implementation of whole-exome sequencing in participants with colorectal cancer or polyposis	adult	germline and tumor	exome sequencing	known disease	genetic counselor and/or medical geneticist
NextGen: Understanding the Impact of Genome Sequencing For Reproductive Decisions	Kaiser Permanente,* Oregon Health & Sciences University, Seattle Children's Hospital, University of Washington	integrating whole-genome sequencing for preconception carrier status and secondary findings into clinical care	adult	germline	genome sequencing	seemingly healthy	genetic counselor
PediSeq: Applying Genomic Sequencing in Pediatrics	Children's Hospital of Philadelphia,* University of Pennsylvania	examining the use of whole-exome and whole-genome sequencing in five heterogeneous disease cohorts: bilateral sensorineural hearing loss, intellectual disability, nuclear-encoded mitochondrial respiratory-chain disorders, platelet-function disorders, and sudden cardiac arrest and/or death	adult and pediatric	germline	exome and genome sequencing	known disease	genetic counselor and/or medical geneticist, cardiologist, hematologist, neurologist

[a]Asterisks denote lead institutions.

Table 2. CSER Consortium R-Awards

Project Name	Institutions[a]	Project Goal
Challenges of Informed Consent in Return of Data From Genomic Research	Columbia University*	developing a menu of approaches to deal with the challenges of informed consent for genomic research
Disclosing Genomic Incidental Findings in a Cancer BioBank: An ELSI Experiment	Mayo Clinic,* University of Minnesota, University of California, San Francisco	determining how to manage return of results and secondary findings to family members, including after the death of the research participant
Impact of Return of Incidental Genetic Test Results to Research Participants in the Genomic Era	Columbia University*	investigating preferences of participants enrolled in genomic research about the disclosure of incidental genetic test results and the psychosocial and behavioral impact of these disclosures
Innovative Approaches to Returning Results in Exome and Genome Sequencing Studies	Seattle Children's Hospital*	comparing traditional results-disclosure sessions (with a genetic counselor and over the phone) with an innovative web-based tool
Presenting Diagnostic Results from Large-Scale Clinical Mutation Testing	Cleveland Clinic,* Mayo Clinic	examining participant and professional understandings of diagnostic results from large-scale clinical mutation testing and attitudes toward testing
Return of Research Results From Samples Obtained for Newborn Screening	Johns Hopkins University*	evaluating current existing state policies regarding the storage of dried blood spots after newborn screening and associated research use to develop policy recommendations
Returning Research Results in Children: Parental Preferences and Expert Oversight	Boston Children's Hospital*	exploring research-participant preferences in the return of individual genomic research results and how this might be incorporated into registry and/or biobank research structure
Returning Research Results of Pediatric Genomic Research to Participants	Vanderbilt University,* McGill University, Baylor College of Medicine, University of Chicago	exploring legal issues raised by the return of genomic research results in minors
The Presumptive Case Again Returning Individuals Results in BioBanking Research	Children's Mercy Hospital*	analyzing claims that the return of bio-repository results is morally obligatory or permissible in genomic research

[a]Asterisks denote lead institutions.

The CSER consortium has worked to improve participant care by exploring variant assessment[26,27] and by comparing approaches across the sites. Early efforts in CSER sites[9] helped to inform the working group of the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) in developing current annotation guidelines.[28] To evaluate whether the published ACMG-AMP guidelines improve the consistency of variant classification across sites, a second exercise has focused on intra- and inter-laboratory differences by applying laboratory-specific and ACMG-AMP variant-classification criteria for 99 germline variants. Variant classification based on the ACMG-AMP guidelines was concordant with each site's prior laboratory-specific variant classifications 79% of the time (intra-laboratory comparison); however, only 34% of the variant classifications were concordant in inter-laboratory classifications (see Amendola et al.[29] in this issue of the *American Journal of Human Genetics*). For the inter-laboratory comparison, it made no difference whether the laboratories used their own prior criteria or the ACMG-AMP guidelines, suggesting subjectivity in the application of the ACMG-AMP guidelines; however, the guidelines were useful in providing a common framework for facilitating resolution of differences between sites. After consensus efforts, 70% concordance was achieved, and only 5% of variants had differences that might affect clinical care. These findings will contribute to future iterations in current ACMG-AMP guidelines and improve and standardize the classification of variant pathogenicity.

Comparison of sequenced variants classified as pathogenic and likely pathogenic by the different U-award sites is instructive, especially in light of the different sets of genes and variant-classification levels that each site selected in reporting their secondary findings. For example, some sites used only small and focused sets of genes that met actionability criteria in advance of sequencing, whereas other sites started with broader lists of thousands of genes and then reviewed the gene-level information alongside the variant-level information when a potentially pathogenic variant or novel loss-of-function variant was identified in the gene. As a result, among participants sequenced across the CSER consortium, comparisons of the rate of secondary findings at each site are difficult.[10] Similarly, the decision to return any pharmacogenomic information or recessive carrier status also varied across sites by design (e.g., one site focused exclusively on the latter). As of the latest reported individual-level data, 3,296 participants have been sequenced and have received their sequencing results. Among sites disclosing any pharmacogenomic information (n = 4), 32.3%–100% of sequenced participants received information about one or more variant(s)

Table 3. Cross-Consortium Collaborative Working Groups

Group Name	Project Goal	Significant Findings	Working-Group References
Actionability and Return of Results (Act-ROR)	defining the principles and processes guiding the definition of "actionable gene" across the consortium, including outcomes and discrepancies; developing variant-classification consensus; developing best practices for analysis and communication of genomic results	defining an "actionable" gene by developing consensus regarding variant classification and developing decision support resources around actionability; developing guidance for classification of secondary findings	Amendola et al.,[9] Berg et al.,[10] Jarvik et al.[11]
Electronic Health Records	understanding and facilitating collaboration related to the integration of genomic information into the EHR, decision support, and linkage to variant and knowledge databases	understanding and facilitating cross-site collaboration, EHR integration, decision support, and database linkage; analyzing the current state of the EHR among six CSER sites, as well as presenting genetic data within the EHR among eight sites; ascertaining current display of genetic information in EHRs; defining priorities for improvement	Shirts et al.,[12] Tarczy-Hornoch et al.[13]
Genetic Counseling	investigating current genetic-counseling topics related to whole-exome and -genome sequencing, including but not limited to recruitment and enrollment, obtaining informed consent, returning sequencing results, and interacting with participants and families in both research and clinical settings	analyzing CGES topics related to genetic counseling, including informed-consent best practices and lessons learned from returning results	Tomlinson et al.,[14] Bernhardt et al.,[15] Amendola et al.[16]
Informed Consent and Governance	discussing emerging issues and developing new and creative approaches related to informed consent in the sequencing context; developing standardized consent language; analyzing experience with institutional governance of genomic data	analyzing CSER approaches to informed consent for the return of genomic research data; supporting the development of new and creative approaches to consent, including best practices and standardized language and protocols; compiling CSER experiences with institutional governance of genomic data	Henderson et al.,[17] Appelbaum et al.,[18] Koenig[19]
Outcomes and Measures	identifying priority areas for investigating psychosocial, behavioral, and economic outcomes related to genome sequencing; coordinating measurement of key outcomes across CSER sites; identifying research strategies to generate evidence to inform health-care policies	examining participant outcomes to inform conversations regarding the efficacy and harms of sequencing, as well as the costs and impacts of genomic sequencing on the health-care system	Gray et al.[20]
Practitioner Education	exploring the growing need for medical genetics education materials for health-care practitioners	newly formed workgroup aimed at exploring the unique educational needs of health-care providers; currently compiling and assessing available resources and looking for gaps and avenues for using expertise and shared experiences within CSER to aid in practitioner genomic education and application	–
Pediatrics	exploring and attempting to develop standardized approaches to address the unique ethical, legal, and practical challenges related to returning results in studies involving pediatric populations	deeply analyzing the issues related to childhood genomic sequencing, including comparing current guidelines and examining ethical responsibilities and recommendations for a future framework for genomic sequencing in children	Clayton et al.,[21] Brothers et al.[22] McCullough et al.[23]
Sequencing Standards	developing and sharing technical standards for sequencing in the clinical context; developing best practices for genomic sequencing and variant validation	analyzing clinically relevant genomic regions that are poorly covered in CGES across ten CSER sites to learn more about target areas for future improvement; developing tools and processes to allow standardized analyses of poorly covered regions at other clinical sequencing centers	–
Tumor	exploring the unique technical, interpretive, and ethical challenges involved in sequencing somatic cancer genomes	educating the oncology community regarding the spectrum of potential tumor sequencing results, as well as secondary findings from germline sequencing and revelations of true germline findings from tumor sequencing	Parsons et al.,[24] Raymond et al.[25]

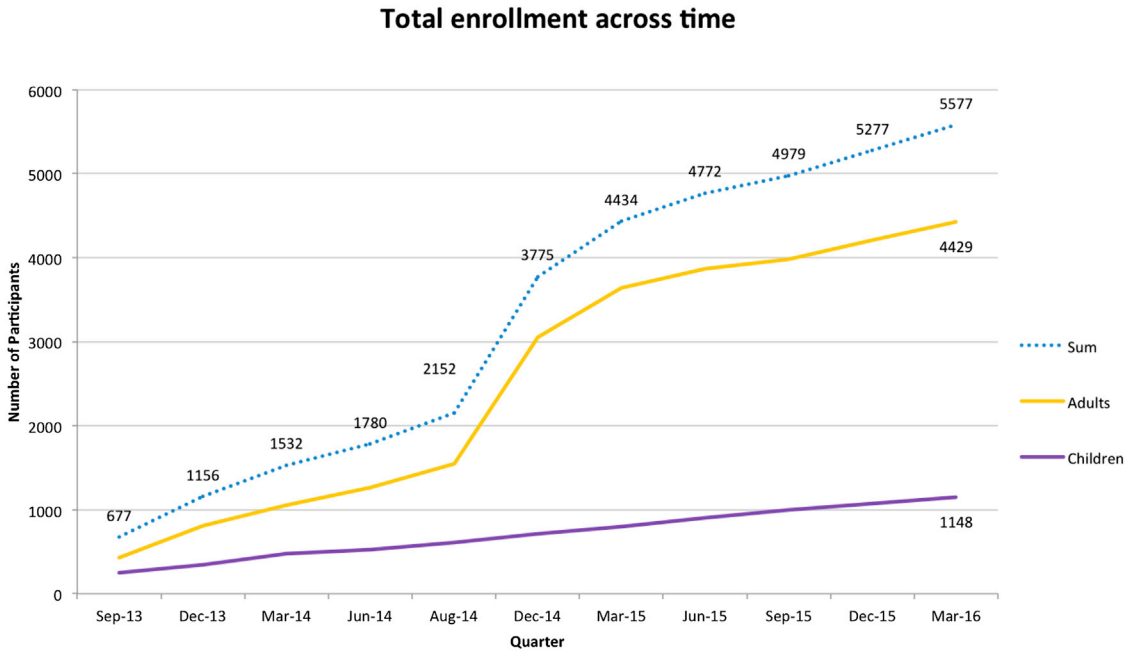

Figure 2. Cumulative Enrollment and Sequencing of Participants in the CSER U-Awards
These numbers reflect participant enrollment (including physician enrollment at some sites). Several sites (MedSeq, CanSeq, and NextMed) enrolled control participants (who were not sequenced) in a randomized trial.

related to pharmacogenomic response. 2%–92% of participants have received information about recessive carrier variants, and this wide range is due to differences in the number of genes considered for return at each site. When just the genes recommended by the ACMG for secondary result return were examined,[30] 68 of the 3,296 (2.1%) CSER research participants were reported to have a pathogenic or likely pathogenic variant in at least one of these genes unrelated to the primary test indication; site-specific percentages varied from 0.28% to 6.52%. This variation can be attributed to a variety of factors, including differences in variant-classification methods,[29] small sample sizes at many of the sites, and the fact that some sites report only pathogenic findings, whereas others report pathogenic and likely pathogenic findings and even variants of uncertain significance. Also, some sites report only on a subset of the 56 ACMG genes, such as genes associated with cancer predisposition.

The variant-interpretation project described above is now helping to bring more consistency to the variant-classification process across sites. In addition, the CSER consortium is working with sites to submit all of their classified variants to ClinVar to improve variant-classification comparisons with other submitters and identify differences that can be resolved. As of the latest reporting, over 2,795 classified variants have been submitted to ClinVar by the CSER sites, making CSER one of the top 20 submitters to ClinVar. Additionally, individual-level datasets containing genotypes and phenotypes from over 2,401 individual-level datasets have been submitted to dbGaP.

Implementation of Clinical Sequencing in the CSER Consortium

Among the four CSER sites conducting sequencing in cancer participants, the BASIC3 trial has presented preliminary data showing that nearly 40% of pediatric participants with solid tumors have potentially actionable mutations when the results of tumor and germline exome sequencing are combined.[31] CanSeq has focused on enrolling participants with advanced colorectal and lung cancer, of whom 88.4% were found to have actionable or potentially actionable somatic genome alterations, whereas the Michigan Oncology Sequencing Center (MI-ONCOSEQ) has identified clinically relevant results from tumor sequencing in 60% of adult and pediatric cancer participants.[32] Both the CanSeq and MI-ONCOSEQ projects have implemented production-scale exome sequencing from archival tissue samples, and the latter program is pioneering an exome-capture transcriptome protocol that improves performance on degraded RNA.[33] The NEXT Medicine study has incorporated exome germline sequencing through a randomized trial to examine care outcomes in participants with hereditary colorectal cancer and/or polyps.[34]

CGES has also been utilized in the diagnosis of numerous suspected genetic conditions. For six disease cohorts that have undergone exome sequencing in PediSeq, the diagnostic rates have varied from 6% in platelet disorders to 20% in sudden cardiac death to 50% in intellectual disability.[35] PediSeq has also created phenotype and pedigree capture technologies, including the use of phenotypes

Table 4. Yield of Variants Related to Phenotypes in Sequenced Symptomatic U-Award Participants

Clinical Characteristics	Sample Size[a]	Percentage of Participants with at Least One Finding (Median No. of Variants Reported)			
		P or LP	VUS	Single Recessive[b]	Other
Germline cancer (all)	1,142	6.2%(1)	36% (1)	2.4% (1)	0.4% (1)
Syndromic ID or autism	431	19% (1)	13% (1)	0.7% (1)	1.2% (2)
Other DD and ID	50	28% (1)	28% (2)	14% (1)	0%
Cardiomyopathy	104	27% (1)	28% (1)	0%	1.0% (1)
Other cardiovascular	274	5% (1)	11% (2)	0%	0.4% (1)
Ophthalmology	80	39% (1)	16% (1)	7.5% (1)	0%
All other characteristics	137	18% (1)	28% (1)	19% (1.5)	2.2% (1)

Abbreviations are as follows: DD, developmental delay; ID, intellectual disability; P, pathogenic; LP, likely pathogenic; and VUS, variant of uncertain significance.
[a]This table does not account for 1,863 healthy individuals within CSER.
[b]Individuals with a single recessive mutation in a gene related to the described phenotype.

to prioritize gene interpretation[36] and the pedigree-drawing program Proband, an app with over 1,700 downloads to date. NCGENES and the HudsonAlpha sites both enroll children with intellectual disabilities and have both observed similar variations in diagnostic rates. NCGENES includes participants with a broad range of diseases; diagnostic rates range from 21% in familial cancer to 39% in children with dysmorphic features to 58% among individuals with retinopathy.[37] The MedSeq project, one of three randomized trials within the CSER consortium, is exploring the potential advantages of whole-genome sequencing (WGS) in participants with cardiomyopathy and has found that WGS robustly confirms diagnoses previously made by next-generation cardiomyopathy panels and occasionally identifies previously undetected etiologic candidates in participants who were not diagnosed by panel testing.[38]

In an attempt to quantify the importance of secondary findings, the NCGENES site created a semiquantitative "binning" metric[39,40] (versions of which have been broadly adapted by other efforts).[41,42] NCGENES reports the frequency of discovering a medically actionable secondary finding to be 3.4%. NEXT Medicine, in conjunction with the Actionability and Return of Results working group,[10] defined a large list of genes for medically actionable conditions and estimated that 0.8% of individuals of European ancestry and 0.5% of individuals of African-American ancestry would be expected to have a pathogenic variant returned as an incidental finding from exome sequencing.[9] PediSeq reviews variants in a list of nearly 3,000 genes and returns secondary findings for risk of Mendelian disease in 10%–15% of participants and carrier findings in nearly 90% of participants. The MedSeq project worked collaboratively with Clinical Genome Resource (ClinGen)[26,41] to apply a method for gene-disease validity classification to evaluate which of the approximately 4,500 disease-associated genes analyzed to date have sufficiently strong evidence for returning variants. The BASIC3 study utilizes the ACMG list of 56 genes plus additional actionable genes evaluated by the project 2 team and has an overall secondary-findings rate of 4.8%.[2]

Although secondary findings in the context of diagnostic sequencing represent a kind of "opportunistic screening,"[3,43,44] several sites have explored the use of sequencing in persons without a suspected genetic condition, a model closer to actual population screening. ClinSeq, the NHGRI intramural program, has treated non-diagnostic sequencing as a hypothesis-generating methodology to report on the implications of secondary findings associated with heart disease,[45] malignant hyperthermia,[46] diabetes,[47] a form of arrhythmia,[48] and the discovery of a late-onset neurometabolic disorder.[49] After identifying loss-of-function variants in genes for which haploinsufficiency is associated with disease, ClinSeq investigators followed up with in-depth phenotyping to reveal that roughly half of the population carrying such variants had subtle phenotypes of underlying genetic disease but were unaware of this.[50] Similarly, the MedSeq project has returned pathogenic variants, likely pathogenic variants, and even suspicious variants of uncertain significance in healthy middle-aged adult volunteers to their primary-care physicians and cardiologists by using a single-page summary of whole-genome results.[26,51] This report categorizes risk variants for monogenic diseases (in genes associated with dominant disease or in genes associated with autosomal recessive disease and in which biallelic pathogenic and likely pathogenic variants have been identified), recessive carrier variants, pharmacogenomic variants, SNP-based risk scores for common cardiovascular conditions, and variants that characterize red blood cell and platelet antigens.[26,38,51–53] BASIC3 and CanSeq are enrolling large teams of pediatric and adult oncologists who receive exome sequencing results and disclose them to families of pediatric cancer participants and adult cancer participants. The primary-care physicians in MedSeq and the oncologists in CanSeq do not have formal genetics training, but in the case of MedSeq, they have been given a brief training module to assist them in interpreting and

acting on the genome reports.[38,51] In MedSeq, both providers and sequenced participants (along with control individuals who are not sequenced) are studied through surveys, interviews, and close monitoring of electronic health records (EHRs), yielding insights about physician preparedness for CGES.[54–57]

Several U-award sites are returning carrier status in addition to monogenic secondary findings. For example, both the MedSeq project and the NCGENES study include carrier results as additional findings in adult participants. The NextGen study is a randomized trial directly investigating the implementation of carrier screening to aid reproductive decision making in adults not known to be a carrier of genetic disease. Focus groups exploring participant and clinician perspectives have shown that potential participants have differing degrees of interest in learning their carrier status,[58] and of those enrolled so far, 71% have at least one carrier result, and 89% of participants are choosing to receive results in one of four optional categories (serious, moderate, adult-onset, and unpredictable). The ClinSeq study is also conducting a randomized trial comparing the return of carrier results through standard-of-care counseling and that through a web site to assess the impact of counseling approach on the cost of genomic health care.

Outcomes and ELSI Issues in Clinical Sequencing

The main results from many of the projects have not yet been analyzed or published because enrollment is still ongoing for some of the projects. However, the CSER consortium is already providing insights into medical, behavioral, psychosocial, and economic outcomes related to the growing use of genomic data in the clinic.[20,59,60] The consortium's Outcomes and Measures working group has identified common research priorities, developed instruments to facilitate data harmonization, and initiated cross-site aggregate and comparative analyses.[20] The inclusion of investigators with expertise in normative and legal ELSI analyses provides additional assurance that best practices based upon CSER data will not only be based on evidence but also be ethically and legally sound.

A major focus to date has been the disclosure of secondary genomic findings to participants. Early findings, based on qualitative, quantitative, and mixed-methods research, suggest that participants and research participants queried during the informed-consent process are usually receptive to learning such findings but that preferences are influenced by the precise nature of the findings, how the offer is made, and a number of individual participant attributes.[59,61–67] For example, in the NCGENES study, adult participants are randomized to either a "control" group or a "decision" group, participants in the latter of which are asked to decide whether they wish to receive any of the six categories of non-actionable secondary findings. Whereas the majority in the "decision" group initially stated an intention to request all secondary findings, fewer than one-third actually requested one or more, demonstrating a difference between hypothetical and real-world actions.

The CSER consortium's empirical studies of clinicians' and genomic researchers' attitudes about disclosing secondary genomic findings show that although few have significant experience in returning such findings, most report that they are motivated to do so in at least some circumstances.[55,68–70] At the same time, CSER studies highlight the many complexities, both normative and practical, that invariably enter into decisions about whether, when, and how such findings should be made available.[43,69,71–77]

The CSER consortium has also addressed the challenges involved in obtaining informed consent for clinical sequencing, including tailoring approaches that are best suited to specific clinical contexts. The consortium has published an empirical analysis of the consent forms used at six U-award sites and three R-award sites, along with recommendations for ways in which consent forms can be improved.[17] CSER investigators have defined four models of consent for the disclosure of secondary findings,[18] identified seven discrete challenges representing gaps in genome sequencing knowledge and faced by genetic counselors,[78] and provided illustrative case examples of practical issues involved in consent and disclosure decisions,[79,80] all suggesting an expanded future role for genetic counselors.[14–16,81,82]

Through its Pediatrics working group, CSER has focused considerable attention on genomic sequencing in children.[21–23] Several site-specific publications have addressed the appropriate role of children in decision making,[83–85] preferences of genetic professionals regarding the disclosure of findings in pediatrics,[68,70,86] limitations in parents' understanding of choices regarding receipt of their children's findings,[87] and certain unique features of informed consent in pediatric oncology.[79]

CSER investigators have also conducted important legal and regulatory analyses relevant to clinical sequencing, including the legal liability for disclosure or non-disclosure of findings to patients, research participants, and family members.[88–91] Other topics include the legal implications of incorporating genomic data into EHRs,[92,93] the limitations of current laws and the potential impact of recent changes to federal privacy and laboratory regulations on access to one's genetic data,[94,95] and a comparison of US law and policy and that of other countries on family access to a proband's genomic findings.[96]

Finally, early research has assessed the economic value and cost-effectiveness of returning secondary findings,[97,98] and additional efforts are underway. CSER investigators have highlighted the need for future research in behavioral economics by recognizing that provision of information does not necessarily lead to health benefits. This research will provide insights into participants' and families' responses to genomic information and

downstream impacts on the utilization of health services, both positive and negative, providing strategies for maximizing positive uses of genomic information.[99,100]

Additional Dissemination and Outreach Activities

The CSER consortium has established a shared, real-time community of research sites pursuing common goals in related yet distinct settings. Thus, the value of the consortium goes beyond the individual publications mentioned above. When CSER was initially funded in 2011, each site was challenged to implement clinical sequencing, standardize variant interpretation, reduce sequencing turnaround time, and develop reliable bioinformatics pipelines. Addressing these common challenges among sites has yielded insights that, when synthesized, are becoming relevant to the broader scientific community. For example, sites have adopted different approaches to the analysis of clinical sequencing data, best exemplified by the "diagnostic-gene-list" approach employed by some sites and the "variant-first" approach adopted by others. An ability to compare such analytical approaches continues to inform the entire field in its ongoing efforts to optimize interpretation. More generally, there have been vibrant discussions and sharing of approaches to informed consent, educational materials, and disclosure methods across many CSER sites. More recently, working groups have been exploring approaches to improve sequencing standards, coverage of clinically relevant genes, and variant annotation by using existing and newly adopted ACMG variant-classification guidelines. Looking ahead, CSER will continue to address questions that are best answered across multiple sites and in multiple settings. For example, projects related to the return of carrier status, re-interpretation of results, management of secondary findings, ethical approaches to combining research with clinical care, and downstream costs of genomic testing are underway.

CSER-related interactions often expand to related genome sequencing efforts. For example, CSER investigators are interacting or collaborating with other consortia in the areas of EHR-based phenotyping, genotyping, and integration of results into the EHR (Electronic Medical Records and Genomics [eMERGE]);[101–103] community-based curation of genes and variants (ClinGen);[41] undiagnosed diseases (Undiagnosed Disease Network [UDN]); implementation of genomic testing in diverse settings (Implementing Genomics in Practice [IGNITE]); newborn sequencing (Newborn Sequencing in Genomic Medicine and Public Health [NSIGHT]); ethics (Centers for Excellence in ELSI Research [CEERs]); prostate cancer (Stand Up 2 Cancer [SU2C] and Prostate Cancer Foundation [PCF] international dream team); trials of prospective precision medicine in cancer (National Cancer Institute and Children's Oncology Group Pediatric MATCH study);[104] and the evolving role of the clinical geneticist (Clinical Genetics Think Tank). These inter-consortium interactions vary in nature from informal consultations to resource sharing to joint meetings and publications.[11,12,22,105] CSER is also informing the development of professional guidelines[28,30,106,107] by sharing resources (e.g., gene lists) and serving as a "sandbox" in which early implementation can be assessed. Other dissemination activities include the release of open-source software,[108] deposition of data into ClinVar and dbGaP, and being a part of high-profile sessions at national medical and bioethics meetings. Study-specific resources such as consent forms, study protocols, educational materials, and sample reports are made publicly available at the CSER Coordinating Center's website (see Web Resources for links to these groups).

Efforts to facilitate outreach to individuals and communities outside academic medical centers have also been implemented. By initiating collaborations with rural and underserved populations, some sites are establishing broader availability of genome sequencing, extending its clinical reach outside of academia and facilitating robust participation by underserved minority groups. Sites interacting with state government agencies that serve families of special-needs children or comprising integrated delivery systems are using their CSER experience as a platform to educate the public and stakeholders who make coverage decisions.

Future Directions for the CSER Consortium

Through its combination of individual scientific enterprise, practitioner participation, and collective synergy, the CSER consortium is uniquely poised to fill some of the most important evidence gaps in the implementation of genomic medicine. Looking toward a future with widespread evidence-based and equitable availability of genomic medicine, there are critical challenges in terms of implementing technical refinements, including accessibility to individuals of diverse ethnic and socioeconomic backgrounds and the attainment and demonstration of desired medical outcomes. In particular, CSER sites can be expected to further advance analyses of observed differences in variant interpretation in concert with ClinGen[41] and to identify new approaches for calling structural variation from next-generation sequencing data. Finally, the genomics regulatory arena is very dynamic with evolving FDA oversight[109,110] and proposed changes to the Common Rule. The CSER consortium has and will continue to play an important role in evaluating and communicating the impact of this rapidly evolving area in topics such as consent and disclosure.

The CSER consortium, along with all genomics investigators, must also consider whether and how genomic medicine might exacerbate disparities in health and health-services utilization to ensure that the intended benefits of genomic medicine are justly distributed.[111] There are several reasons why poor, rural, and racial and ethnic minority populations might be less likely to realize

tangible health-related benefits as genomic medicine becomes more commonplace. Existing databases of disease-associated genes and variants are overwhelmingly drawn from individuals of European ancestry, and populations of non-European ancestry have patterns of genetic variation that are not yet well characterized in control populations. This lack of data complicates the interpretation of novel and rare variants. Also, historical and continuing social disparities in health-care access, health-insurance coverage, and community engagement and trust are heightened by issues raised in genomics. Without concerted intervention, these converging forces threaten to perpetuate and expand current health disparities in ways that might disadvantage members of racially and ethnically diverse communities for decades. A number of sites within the CSER consortium have begun expanding their enrollment of minority ethnicities to begin addressing these inequalities and will continue to identify relevant opportunities.

More formal studies in comparative effectiveness and cost-effectiveness are necessary for answering questions about whether and under what circumstances sequencing should be applied and for guiding third-party payment for clinically helpful genomic services. The degree to which the identification of secondary findings and the sequencing of asymptomatic individuals might lead to downstream health benefits and incur or offset downstream costs will be critical. Deeper phenotyping of apparently pathogenic variants in participants who do not show symptoms of an associated genetic condition will be required and will provide key information on the classification of variant pathogenicity, penetrance estimation, and the identification of modifying or protective factors that could provide important insights into future treatment of rare or even common conditions. But with iterative and more in-depth phenotyping and the use of tools ranging from wearable monitoring devices to microscopic processes in cell culture, there is an opportunity to define disease and diminished function in entirely new ways. As medicine enters an era where sequencing and other -omics can be applied routinely, the CSER consortium is helping to accelerate the realization of preventive and precision medicine.

Supplemental Data

Supplemental Data include three Supplemental Notes and can be found with this article online at http://dx.doi.org/10.1016/j.ajhg.2016.04.011.

Consortia

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Conflicts of Interest

R.C.G. has received compensation for advisory services or speaking from Invitae, Prudential, Illumina, AIA, Helix, and Roche. L.G.B. receives royalties from Genentech and Amgen Corporations and is an uncompensated advisor to Illumina. W.K.C. is a consultant for BioRefrence Laboratories. L.A.G. is a consultant for Foundation Medicine, Novartis, and Boehringer Ingelheim, is an equity holder in Foundation Medicine, and is a member of the scientific advisory board at Warp Drive. He receives sponsored

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Web Resources

Centers for Excellence in ELSI Research (CEERs), http://www.genome.gov/27561666

Clinical Sequencing Exploratory Research (CSER) consortium, https://cser-consortium.org

CSER organizational chart, https://cser-consortium.org/system/files/attachments/cser_organizational_chart.pdf

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

Implementing Genomics in Practice (IGNITE) Network, http://www.ignite-genomics.org

Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT), http://www.genome.gov/27558493

Stand Up 2 Cancer (SU2C) and Prostate Cancer Foundation (PCF) international dream team, https://www.standup2cancer.org/dream_teams/view/precision_therapy_for_advanced_prostate_cancer

Proband, http://probandapp.com

Undiagnosed Disease Network (UDN), http://www.genome.gov/27550959

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The American Journal of Human Genetics, Volume *98*

Supplemental Data

Clinical Sequencing Exploratory Research Consortium:

Accelerating Evidence-Based Practice of Genomic Medicine

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Supplemental Note: Focus and Progress of Individual U-Award Projects

Children's Hospital of Philadelphia (CHOP; PediSeq)

The CHOP/UPENN Pediatric Genetic Sequencing Project (PediSeq) is working to optimize methods for bringing genomic sequencing into a pediatric clinical setting. We are focused on 6 genetically heterogeneous cohorts: bilateral sensorineural hearing loss, sudden cardiac arrest/death, intellectual disability, autism, platelet function disorders and nuclear encoded mitochondrial respiratory chain disorders. The primary goals of this project are: 1) to establish the study infrastructure and pipeline to validate a practical genomic sequencing approach in pediatrics; 2) to generate genome-scale sequence data for cohorts of uniformly phenotyped subjects for assessment and decision support for presenting actionable genomic findings to clinicians, patient participants, and families and 3) to evaluate the informed consent process for genomic sequencing from the perspective of parents and the provider obtaining consent to explore and understand the impact of genomic sequencing results from the perspective of patient participants, parents and providers.

To date, the PediSeq Project has designed and implemented a pipeline to identify, interpret and report medically relevant exome sequencing (ES) results to families and physicians, and created a comprehensive summary report, and allied online educational support modules, for primary variant findings (related to the indication for testing in our 6 cohorts) as well as secondary findings (that are immediately medically actionable, medically actionable in childhood and adulthood and carrier status). Through the PediSeq project has developed several new tools for phenotype capture and analysis have been developed including the Proband pedigree drawing program (now available in the Apple app store and widely used in a number of academic medical genetic programs) as well as a prototype algorithm that uses phenotypic information in gene

prioritization.[1] We have enrolled 200 families, evaluated sequence issues related to coverage and use of gene lists and have identified a positive result in 6-50% of probands (6% in the disorders, 20% in sudden cardiac death, 23% in sensorineural hearing loss and 50% in intellectual disability) with a VUS rate in these cohorts ranging from 38 (intellectual disability) to 67% (sudden cardiac death).[2] Secondary findings analysis includes a gene list of 2956 genes and our positive findings range from 10-15% for immediately medically actionable conditions and 83-88% for carrier status. We are focused on completing our analyses of informed consent data to understand patient participant and provider experiences with informed consent for genomic sequencing in pediatrics in addition to collecting post-results survey and interview data, and the dissemination of research across the CSER Consortium. To date, we have analyzed over 50 audio-recorded informed consent (IC) sessions to understand patient participant and provider experiences with informed consent for genomic sequencing in pediatrics. We are collecting audio recordings from return of results sessions, which are being transcribed and analyzed, post-return of results survey and interview data from parents, adolescents and primary care providers have been initiated.[3, 4] In analysis of the thematic and contextual elements in IC sessions where an adolescent proband has the cognitive capacity to participate in decision-making, we found that 1) there is considerable variability in the degree of adolescent involvement in the IC sessions, with older children more engaged in the session and more likely to be consulted by parents and providers for their opinions, and 2) several adolescents and young adults felt unprepared to make decisions about adult-onset secondary findings and looked to parents for guidance, and parents tended to take on protective roles, advising and cautioning their children.

PediSeq investigators have been involved in or led several cross-consortium working group activities.[3-7] The work on the PediSeq project and interactions across the

CSER consortium and the medical genetics community have formed a Clinical Genetic Think Tank of over 50 participants that met twice and have produced a white paper with practical recommendations for the implementation of genomic diagnostics into the clinical work flow. PediSeq has also informed practices for the creation of the Division of Genomic Diagnostics, with input from PediSeq to the exome sequencing test launched last year at CHOP.

PediSeq continues to optimize pediatric sequencing workflow and variant calling algorithms as well as to develop a decision support system for delivering genomic variants and interpretation into the EHR.

University of North Carolina at Chapel Hill (NCGENES)

NCGENES focuses on critical questions that must be addressed before genome-scale sequencing is routinely incorporated in medicine, including the diagnostic yield of whole exome sequencing (WES) in diverse clinical settings, the incidence and impact of secondary findings, participant attitudes towards secondary findings and the development of practical schemes for the holistic classification of genomic variants. Another major goal is optimizing minority enrollment to ensure social justice and improve genomic variant interpretation.

NCGENES has completed analysis of over 620 participants. An overarching question for any medical test is determining the clinical situations in which it should be applied. Accordingly, NCGENES is assessing diagnostic yield of WES in a variety of clinical settings spanning 7 diagnostic categories. Yields of possible or definitive diagnoses vary significantly. For example, the yield for cardiomyopathy is 53% and retinopathy 58%,[8] establishing WES as a viable diagnostic approach in such conditions. The yields for neurological disorders and dysmorphology are 36% and 39%, respectively, while WES in participants with apparent familial cancer yields a reportable

result in only 21% of those sequenced, demonstrating that WES adds little to standard approaches in this setting.

Assessing medical actionability of genes is critical when applying WES to participants, given the certainty of generating secondary results that may or may not be necessary to return. To deal with this central problem, NCGENES created a semi-quantitative "binning" metric[9] (now broadly adapted by other efforts such as ClinGen,[10] and EGAPP[11]). The NCGENES experience reveals that thus far, the rate of discovering a medically actionable secondary finding is 3.4%. To address the problem of whether and how to offer non-medically actionable secondary findings, NCGENES employs a study design that ascertains subjects' real-world choices to request such findings. Our results suggest that prior hypothetical studies overestimated the value such results hold for individuals: when a small (but realistic) barrier such as the need to make a phone call is implemented, interest in non-actionable results is considerably lower than participants' initially stated preferences and hypothetical estimates previously reported in the literature.

Our knowledge about the genomes of minority populations has lagged behind that of populations with European ancestry, with important implications for broad and just implementation of genomic medicine and the clinical interpretation of variants. Thus, a major aim of NCGENES has been to emphasize minority participation, currently 25.8% (14.1% AA, 8.9% Hispanic, 1.6% Native American, 1.2% Asian), although participation drops disproportionately, from initial enrollment through return of results and completion of final surveys. Strategies that have facilitated minority participation in NCGENES include geographically convenient clinics, reimbursement for even small expenditures by participants, working with well-established community groups, and offering accessible language resources.

Brigham and Women's Hospital/Harvard Medical School/Baylor/Duke (MedSeq Project)

The MedSeq Project is exploring the application of whole genomes sequencing and its rapid interpretation to provide maximal benefit in terms of both the indication for testing of a genetic condition (in this project, cardiomyopathy) and population screening of healthy individuals. It is also examining the impact of communicating secondary findings to clinicians within the currently existing medical model, and carefully tracking medical, behavioral and economic outcomes using a randomized, controlled trial design.[12]

Thus far, the MedSeq Project has designed and implemented a pipeline to identify, interpret and report medically relevant whole genome sequencing (WGS) results to physicians,[13, 14] and created a one-page summary report on monogenic disease variants, carrier status, pharmacogenomic findings and genetic liability for common complex diseases that even primary care physicians can understand and utilize in the care of their patient participantss.[15] We have found that 21% or our participants had an unanticipated finding of a pathogenic variant for a monogenic disease and 92% had at least 1 pathogenic variant for a recessive disease. Of the participants who had a known cardiomyopathy variant before or at study start, 95% (19/20) were confirmed by WGS and reported on the MedSeq Genome Report. Of those who did not have a known cardiomyopathy variant, 1 new pathogenic variant and 4 new variants of unknown significance in cardiac genes were identified as potential causes of the cardiomyopathy. We have also demonstrated how, for a minor increase in cost, red blood cell and platelet antigen prediction can become a routine part of WGS result reporting, informing clinical care decisions and providing important information for blood donation.[16] We have determined the feasibility of preparing non-geneticist physicians to use WGS in clinical care through a combination of upfront education and ongoing support.[17-21]

Early interactions between MedSeq Project investigators and collaborators in the CSER Consortium informed the development of the ACMG gene list for secondary findings and subsequent commentaries.[22-26] Importantly several investigators substantively contributed to foundational articles that are helping to set clinical standards for clinical sequencing.[27-31] MedSeq investigators, along with other CSER site investigators, have contributed significantly to the working groups that developed new ACMG standards for next generation sequencing,[32] variant classification,[33] and laboratory analysis of hearing loss;[34] along with consensus statements on the return of secondary findings in research biobanks,[35] and the return of incidental information to family members of research participants.[36] One group has built on the MedSeq data to analyze the successes and failures of the Genetic Information Nondiscrimination Act for clinical sequencing,[37] and to explore methods for modeling cost-effectiveness of genome sequencing.[38]

Data and experiences accrued in the MedSeq Project and across the CSER Consortium helped support awards in economics and decision science around genomics, pharmacogenomics and a successful application for the BabySeq Project sequencing newborns. In addition we are a site for one of the Mendelian Sequencing Centers, a site for the Undiagnosed Disease Network, an eMERGE III Genomics Center, and one of two Sequencing Centers for eMERGE III.

The MedSeq Project plans to collect additional information about clinical genomic penetrance through targeted phenotyping of those MedSeq Project participants who have received a pathogenic (P), likely pathogenic (LP), or variant of uncertain significance suspected to be pathogenic (VUS-favor path) for a dominantly inherited condition (or biallelic P, LP, VUS-favor path variants for a recessive condition), and to explore the clinical utility of WGS in minority populations by recruiting additional participants to be randomized in the extension phase of the project.

Baylor College of Medicine (BASIC3)

The goal of the Baylor College of Medicine (BCM) CSER project is to incorporate both tumor and germline whole exome sequencing into the care of newly diagnosed pediatric cancer patient participants (focusing on high risk solid tumors including brain cancers) at Texas Children's Hospital in order to determine: (1) the diagnostic yield, (2) potential clinical utility of both tumor and germline findings, and (3) the impact of clinical genomics on physicians and families. In order to complete this study, the Project 2 investigators led the development of the first entirely CLIA-certified clinical whole exome sequencing pipeline for diagnosis,[39, 40] with all components of the sequencing pipeline made publically available followed by development of a cancer whole exome sequencing clinical pipeline. As of September 2015, we have enrolled 20 pediatric oncologists and 230 participants with childhood cancer (as well as parents when available) into the BASIC3 (Baylor Advancing Sequencing in Childhood Cancer Care) trial and 20 pediatric oncologists. We have reported on our consent methodology,[41] which demonstrated high interest of parents and equitable enrollment of families of different population groups from our diverse patient participant population. We have reported key findings at national meetings recently published on the findings from the trial including demonstrating that nearly 40% of pediatric solid tumor participants have potentially actionable mutations when combining results of tumor and germline exome sequencing.[42] The analysis of the baseline interviews of physicians and parents demonstrates that both groups (for different reasons) do not expect integration of WES to be disruptive in the setting of childhood cancer care.[43] The analyses of the physician communication of exome results and their interpretation of their participants' exome results for treatment decisions are in progress. Based on these results we have recently revised our exome disclosure

practice to focus on clinically meaningful results (whether from tumor or germline) and decrease time spent on other findings such as variants of uncertain significance.

BCM investigators have given major presentations and education sessions at national cancer and genetics meetings including the American Society of Clinical Oncology and ACMG, in addition to publishing on the timeliness of implementing clinical genomics[44] and the appropriateness of the ACMG incidental finding recommendations in the setting of cancer testing.[45] The clinical sequencing experience of the Project 2 team has led to BCM becoming a clinical sequencing center for the Undiagnosed Disease Network (UDN) and the eMERGE III consortia as well as being a clinical study site for UDN and a ClinGen site.[10] The National Cancer Institute and Children's Oncology Group have committed to a nationwide prospective precision medicine trial using genetic analyses of tumors at relapse with BASIC3 investigators co-chairing of the germline reporting committee.

Kaiser-Permanente/Seattle Children's Hospital (NEXTGEN)

The NextGen study is investigating the clinical implementation of carrier screening using genome sequencing (GS) to aid reproductive decision-making in healthy adults. The study population includes individuals whose regular provider has already facilitated pre-conception carrier screening for any condition. This is a randomized trial to evaluate outcomes of adding GS versus usual care. Carrier screening is potentially relevant whenever genomic sequencing is used in reproductive aged adults, regardless of the indication for sequencing. This study's focus on individuals with an interest in learning their carrier results will allow us to rapidly assess the potential impact and outcomes of using GS for carrier screening.

We have established an analytic pipeline that includes initial sequencing, tools for sequence alignment and variant calls, variant interpretation, confirmation using

Sanger sequencing, and laboratory report generation. This work contributed to the development of guidelines by the ACMG for variant classification.[33] We have implemented clinical components including genetic counseling, integrating the clinical report into the electronic medical record, and are developing patient-focused materials including key messages to report positive findings and notification of negative findings. Overall, 71% of participants have at least one carrier result, with a range of 1 to 5 results per person, and a median of 1 result.

Our study team has explored patient participant and clinician perspectives on which carrier results to report. Through focus groups, we identified two types of potential participants, “hesitant” and “certain”, who have different perspectives.[46] This has guided our approach to disclose results by providing choices at every point, including the choice to change their mind and not receive results. We also classified conditions into broad categories, which are then used as a tool to understand participant preferences for receiving results. Initial work, guided by expert and focus group participant input, led to the development of a taxonomy with five categories: lifespan limiting, serious, mild, adult onset, and unpredictable. We then conducted a survey to assess whether participants perceive distinctions among these categories and found empirical support for treating these as separate categories, with the possible exception that serious and mild are the most difficult to distinguish.[47] An expert panel has now classified 790 conditions according to this taxonomy. There were a few gene/condition pairs that we decided we will not disclose, due to lack of information in the literature to support the association between the gene and condition. In practice, 91% of participants choose to receive results in all categories, with the adult onset and unpredictable categories most commonly not selected.

A major challenge has been conveying to participants uncertainty associated with variant classifications and their association with clinical disease. Primary questions that

our study was designed to address that remain unanswered include: 1) reactions (e.g., anxiety) to GS, 2) the impact of GS on downstream utilization of care, 3) satisfaction with how the results are delivered, 4) patient participant understanding and comprehension of the results and genetic concepts, and 5) reasons why potential participants might refuse participation in the study.

Dana-Farber Cancer Institute (CanSeq)

The CanSeq Project is a study of prospective germline and somatic WES in participants with advanced lung and colon cancer with return of clinically actionable and potentially actionable results to the patient participant and physician. CanSeq also studies the impact of information derived through WES on cancer patient participants as well as experiences of oncology providers as they implement WES into cancer care delivery.

The CanSeq Project has developed a production-scale platform for WES from archival formalin fixed paraffin-embedded (FFPE) material and implemented these analytic practices in the CLIA sequencing lab at the Broad Institute. It has designed and implemented a post-analytical pipeline for an effective and reproducible approach for the assessment and curation of genome variants and for interpretation and report of genome results. As part of the pipeline, the CanSeq Project developed an evidence-based list of clinically “actionable” alterations and has identified a broad range of biologically and clinically consequential somatic and germline alterations in our participants. As of September 2015, CanSeq has enrolled 211 patient participants and 27 treating oncologists. All patient participants and oncologists are asked to complete a baseline survey and subset of patient participants and oncologists are invited to participate in in-depth qualitative interview shortly after consent. The CanSeq Project has provided detailed sequencing genome reports to the treating oncologists of 155 patient

participants, and has asked all patient participants, and their treating oncologist to complete post-disclosure surveys after sequencing results have been discussed. One of the aims of the ELSI Project (Project 3) was to evaluate the process by which key decision-makers, working collaboratively, evaluate sequencing data and guide the integration of those data into clinical cancer care. In service to this aim, we are also conducting an ethnographic analysis of CanSeq's Cancer Genomics Evaluation Committee.

National Human Genome Research Institute (ClinSeq)

The ClinSeq® Project began in 2006 and joined the CSER Consortium in 2013 (but is reviewed and funded through a distinct mechanism). As a CSER precursor, ClinSeq® piloted several approaches and questions that are being more thoroughly explored across the consortium. Our main focus includes hypothesis-generating clinical research (including secondary findings and predictive medicine), novel modes of returning exome sequencing results, and empirical studies of participant views of sequencing.

The early results on secondary findings from ClinSeq[48] were the primary data that supported the policy development for the American College of Medical Genetics and Genomics (ACMG) report on returning secondary findings.[22] While some elements were controversial, that has now settled, and we believe that ClinSeq and CSER, through these recommendations, have changed the practice of genomic medicine.

Our novel approach has led to new insights on secondary findings including heart disease,[49] malignant hyperthermia,[50] diabetes,[51] a novel form of arrhythmia[52] and discovery of a late onset neurometabolic disorder.[53] Finally, we have generalized this approach to a genome-wide approach, identifying loss of function variants in haploinsufficiency genes, followed by phenotyping[54] Roughly half were positive, which

shows that 3% of the population have an autosomal dominant disorder resulting from these variants, and are unaware of it. We have shown that high penetrance alleles that can be used to predict diseases that are more common than previously known, and the yield for this type of screen is high. Also, it provides a pathway toward larger scale discovery, which we are proposing to pursue through a CSER collaboration to pool our data to allow for further hypothesis-generating research. This will provide CSER with the capability to not only pilot predictive medicine, but to perform discovery as well. CSER is the ideal setting for this effort as it combines the datasets and clinicians who are expert at deep phenotyping of rare diseases, which our efforts have shown are collectively, not rare after all.

The ClinSeq social and behavioral team has described altruistic and personal motivations for undergoing sequencing,[55] high interest in learning results,[56] promising communication and clinical use of returned variants and high perceptions of uncertainty about future results.[56] We have also explored novel constructs to evaluate preferences for the return of results. Our efforts have revealed participants with avoidance of information or forecasting high negative affects avoided learning variant results for both preventable and non-preventable disease risk.[57] Participants perceiving high ambiguity in results are less interested in variants for non-preventable disease and carrier status[58] and those seeking high injunctive and descriptive norms are more interested in receiving all types of results (unpublished data). We are currently completing a randomized controlled trial of return results comparing two delivery modes. Future studies are planned in an African American cohort that is under recruitment.

The ClinSeq investigators initiated a CSER project to develop a taxonomy of uncertainty for genomics information that will be made available as an interactive website for investigators. The taxonomy categorizes the dimensions of uncertainty throughout the sequencing process to promote consistent descriptors of uncertainty to

guide research and clinical care.

HudsonAlpha Institute for Biotechnology

The HudsonAlpha CSER project, conducted with investigators at the University of Alabama at Birmingham and the University of Louisville, and is providing genomic diagnoses to children with intellectual disability, developmental delay, and related phenotypes. We aim to not only diagnosis children with overtly pathogenic variants in well-studied genes, but also to discover novel genetic contributions and the mutational mechanisms, including pathogenic non-coding variants that lead to these phenotypes. We are also examining several more general issues related to the implementation of clinical genomic testing, including: partnering with community-based clinics outside of large academic medical centers to evaluate the psychological effects of genetic results, especially those that are uncertain; and determining how timing of soliciting preferences with respect to secondary genetic results influences the effects of those results.

In pursuit of the above goals, we enroll children with unexplained physical and cognitive disabilities via a pediatric neurology clinic. When available, one or both biological parents are also enrolled. To date, we have enrolled 293 affected probands from 265 families (776 participants) and with overall goal of 450 probands (1,350 participants). While originally based on exome sequencing, we now applying whole-genome sequencing (30x). Results to date indicate the considerable clinical utility of genomic testing in this population, including examples of improvements not only to management of symptoms in probands but also to the psychological well-being of parents. Our results, infrastructure, and experiences with CSER are facilitating dramatic expansions of clinical sequencing at HudsonAlpha along with clinical partners across Alabama and beyond.

University of Michigan (MI-ONCOSEQ)

Initiated in April of 2011, the Michigan Oncology Sequencing Center (MI-ONCOSEQ) project set out to translate and exploit advances in high throughput sequencing towards the development of a "personalized" strategy for cancer. A pilot "proof-of-principle" study was conducted which prospectively enrolled participants with advanced cancers for comprehensive mutational analysis.[59] Subsequently, a number of important discoveries resulted from this analysis including the discovery of a novel gene fusion, NAB2-STAT6 in a rare cancer, solitary fibrous tumor (SFT).[60] We also identified gene fusions involving the *FGFR* gene in diverse cancers, including breast and prostate cancer,[61] several of which are potentially targetable by available therapies.

Under the CSER mechanism, we carried out integrated sequencing (whole exome sequencing of tumor/normal and transcriptome sequencing) to obtain a view of the landscape across of the genetic alterations in individual tumor specimens that can identify informative and/or actionable mutations. Thus far, we have enrolled a total of 333 adult and 99 pediatric participants in the study. Of the 432 enrolled participants, 370 participants have undergone full sequence analysis, for whom a molecular report was returned to the treating physician. Overall, the average turnaround time from sample collection/receipt to return of results to physicians was 62 days. Clinically relevant results were identified in approximately 60% of participants and clinically significant germline aberrations were identified in 26 adults and 10 pediatric participants.

The MI-ONCOSEQ study has resulted in a number of significant research findings. Early on, we reported the activating mutations in *ESR1* that are an important mechanism of acquired endocrine resistance in breast cancer therapy.[62] Our UM team in

collaboration with investigators across the Prostate Cancer Foundation-Stand Up 2 Cancer (PCF-SU2C) Dream Team sites, led a study to develop a precision medicine framework for metastatic, castration-resistant prostate cancer (mCRPC) by obtaining a comprehensive picture of cancer-related mutations and to incorporate this information into therapeutic strategies and/or enrolling subjects into appropriate clinical trials.[63] Recently, we reported the results from 102 pediatric participants enrolled in the PEDS-ONCOSEQ study,[64] the first real-time, integrated genomic sequencing study in children with relapsed cancers. Surprisingly, we found that 10 percent of the participants had an inherited cancer risk potentially impacting multiple family members and these families were referred for genetic counseling. Finally, in order to improve the extractable data from low-quality samples such as FFPE, we developed an exome-capture transcriptome protocol showing greatly improved performance on degraded RNA[65] that enables measurement of absolute and differential gene expression, and of calling genetic variants and detecting gene fusions.

Our long-term goal is to achieve a more clinically feasible turnaround time for sequencing. To close the gap in this area, we have developed a targeted panel that significantly reduces the sequencing timeframe and we are exploring other approaches to narrow the analysis pipelines.

MI-ONCOSEQ included a multifaceted project to consider ethical and psychosocial aspects of patient participants with advanced and refractory cancers undergoing clinical sequencing. A mixed-methods approach - including observations of tumor board proceedings, qualitative interviews with key stakeholders, deliberative sessions, and quantitative surveys of patient participants and referring oncologists - has examined issues involved in the interpretation and disclosure of sequencing results to clinicians and patient participants. Findings to date suggest notable challenges for

informed consent and communication of genomic results, given high expectations of the clinical utility of next-generation sequencing and patient participant preferences for the disclosure of a wide range of secondary findings.[66] Future plans include the development and evaluation of different techniques for educating participants and clinicians about NGS in a cancer context, with a focus on a) effectively managing the high volume of information generated by sequencing and b) conveying both the clinical implications and limitations of test results.

University of Washington\ (NEXT Medicine)

The New Exome Technology in (NEXT) Medicine study is exploring the incorporation of exome sequencing into the clinical care of participants being evaluated for hereditary colorectal cancer and/or polyps.[67] The project's primary goal is to use a randomized controlled trial to evaluate the challenges and potential benefits of using this technology compared to usual care in the clinical genetics setting,[67] with an emphasis on diverse measured outcomes.[68, 69] NEXT Medicine personnel are developing a framework for the return of secondary findings and incorporating these results into the electronic health records (EHRs) of participants, piloting active clinical decisions support, as well as assessing downstream health and economic outcomes.

NEXT Medicine study personnel have established a CLIA laboratory pipeline that provides sequencing and annotation for study participant exomes. A secondary finding gene list has been developed[70] and continues to be revised by the NEXT Medicine Return of Results committee. Variants in these secondary finding genes are interpreted based on a framework established as part of the project, which requires a high threshold of pathogenicity evidence to return a secondary finding variant.[71] Two separate reports are given to participants and placed in their EHR;[72] one for diagnostic findings and one

for secondary findings. To date, 8.4% (7/83) of participants have had an additional diagnostic finding returned by exome sequencing that was not identified by their clinical test. In addition, 2.4% (2/83) of participants have had an actionable secondary finding variant. We have designed and implemented a tool to measure participant preferences.[73, 74] and have shown value in returning actionable secondary findings[68] and using panel testing for colorectal cancer.[68] We have studied and optimized active decision support rules using user centered design principles and working prototypes. We have also developed a process to enter results in a discrete choice format which has enabled piloting and evaluation of active decision support alerts in the EHR for this ongoing study.[75]

The work of the NEXT Medicine study has informed the medical genetics community regarding the likelihood of identifying a pathogenic, medically actionable secondary finding in a genomic test.[71] The NEXT Medicine incidental finding gene list has been shared with the ACMG committee tasked with developing an actionable gene list[22] and other researchers and laboratories providing a reference point for those addressing similar issues incorporating genomic sequencing into clinical practice. These investigators also lead a multi-site consensus paper on return of genomic results to research participants.[5] Their work with EHR vendors and other companies has aided in the prioritization of incorporating genomic information into the medical record in a scalable, usable way.[31, 76] A robust program in legal and regulatory issues[77, 78] related to next generation sequencing has supported the legality of returning certain non-CLIA research results[79] and suggested specific post-market FDA regulations to improve patient safety.[80]

Ongoing work of the NEXT Medicine study includes the discovery of new colorectal cancer and polyp risk genes and variants. Study personnel also explore

participant experiences with receiving exome sequencing results and non-genetics providers' views on integrating genomic sequencing into their clinical practice. The investigators will continue to respond to the dynamic legal and regulatory climate.

Supplemental Note: Focus and Progress of the Individual R-Awards

Boston Children's Hospital

Our R01 grant *"Returning Research Results in Children: Parental Preferences and Expert Oversight"* empirically explores the extent to which participant preferences can reliably guide the return of individual genomic research results in a pediatric setting.

Through an iterative series of interviews with parents, we developed a preference-setting tool that allows participants to choose which results to receive based on the severity and preventability of conditions.[81] The model also allows participant to opt out of receiving results for categories of conditions perceived by parents in our interviews to be highly sensitive – mental illness, developmental disorders, and childhood-onset degenerative conditions – as well as adult-onset conditions not treatable during childhood.

The goals of our study were to test participants' response to biobanks with different return of results policies and a preference setting model, and to use hypothetical research results to determine whether participants fully understand the implications of their stated preferences. We conducted an online survey of parents of children at BCH. Participants were randomized into one of four hypothetical biobanks with different result return policies: "All" results returned; "None" - no results returned; "Binary" - choice to receive all or none; or "Granular" – use preference setting tool to designate types of results to receive. Groups were shown a "Hypothetical Result Report" with results that they may/may not receive based on the group they were randomized to, and on their choices (Binary and Granular only). The Binary and Granular groups were then given the option to reset their preferences. Our initial data suggest that the ability to

designate preferences leads to greater satisfaction and may increase biobank participation,[82] and other manuscripts have been submitted or are in progress.

Finally, we conducted a series of interviews of parents who had received genomic research results on their child to assess the impact of return of research results on families and several key findings are under preparation for publication.

Cleveland Clinic

This 3-year R01 grant aims to develop best practices for "Presenting Diagnostic Results from Large-scale Clinical Mutation Testing". Its goals are to examine patients participants' and genetic professionals' perspectives on the presentation of diagnostic findings from clinical genomic testing. Using a combination of empirical methods, the project seeks to characterize patient participant and provider expectations of clinical genomic testing. In addition, the project will develop a short, 20-item instrument for measuring patient participants knowledge of clinical genetic testing.

The empirical studies proposed for this project were completed in 2013. These included participants' interviews and surveys, focus groups with genetic professionals, and development of an instrument for measuring participants' knowledge. Multiple peer-reviewed publications were produced by members of our study team.[83-87] These publications highlight the complexity of managing diagnostic results produced through highly multiplexed forms of genetic analysis, such as whole-exome sequencing. These studies also highlight a high level of interest in genomic risk profiling among participants seeking preventive health and wellness services. Additional publications are in preparation for publication. In addition to these empirical studies, members of the project team conducted conceptual studies of relevant issues in the adoption of clinical genomics. These studies resulted in multiple keynote presentations at national

conferences and peer-reviewed papers in prominent medical journals.[88, 89] Lastly, in partnership with other CSER Consortium sites, project leaders contributed to jointly authored papers that sought to define best practices for implementing new forms of genomic testing.[5, 90]

Johns Hopkins School of Medicine

The overarching goal of this project is to facilitate the development of the normative and legal framework necessary to return results of genomics research conducted using residual newborn screening dried blood samples (DBS) to the parents of individual research participants. Specifically, the project goals are to identify key gaps in the regulatory framework in which legal considerations related to the return of results of genomics research using DBS have not been fully considered and to develop specific recommendations regarding key elements that need to be addressed by state policy makers in order to implement a system in which results from genomics research with DBS are returned to parents. Careful consideration of these issues is important because newborn screening is a coordinated system of education, screening, follow up, diagnosis, and treatment that requires collaboration between state newborn screening programs and clinical care providers.

A manuscript that explores the circumstances under which returning a subset of results of genomics research conducted using DBS to parents may be beneficial to research participants, state newborn screening programs, and the research enterprise has been published.[91] Significant changes to the newborn screening program infrastructure would be needed to return results of research conducted using DBS to participants' parents. This manuscript explores whether research results should be returned in this context, what types of results should be returned, and by what

mechanism results should be returned. Manuscripts that discuss the lessons learned regarding the development of state policies in the context of historical experience with the expansion of newborn screening and the development of biorepositories using DBS and the ethical obligations of researchers to return unanticipated research results to infants' parents currently are in preparation.

Columbia University

The Columbia R01 Award has been examining research participants' preferences for learning secondary findings from genomic research studies. Two hundred and nineteen genetic research participants (38% response rate) completed a questionnaire on their preferences to learn about 11 categories of secondary findings including ancestry, pharmacogenetics, carrier status, and secondary findings associated with a personal disease risk of variable severity and penetrance. The majority (73%) of respondents indicated that they wanted to learn all results. There were only four types of secondary findings (depression, Alzheimer's disease, Huntington's disease and pancreatic cancer) for which more than 10% of respondents indicated they would not want to receive results. Respondents who reported higher levels of concern about genetic secrecy or had no college education were less inclined to request all results. There was a modest correlation between respondents who had children affected with a medical condition and not wanting to learn all results. In our interim analysis we have found no difference in the psychosocial and behavior measures administered pre-test and one month post disclosure including no difference in depression or anxiety. The genetic counselor for the study, reflected on her experience of obtaining consent and disclosing genomic results as part of this study, including the importance of an

interactive, patient participant -centered counseling model to facilitate informed patient participants choices.[92]

We have also assessed genomic researchers' perspectives on the return of secondary findings to research subjects. We found that researchers in general support the return of secondary findings but had concerns about the potential burdens it may have on research.[93] Support for returning certain types of results was correlated with the clinical experience of the researcher.[94]

Mayo Clinic/University of California- San Francisco/University of Minnesota

This 5-year R01 on "Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment",[95] funded by NCI and NHGRI, combines empirical and normative bioethics methods to address the question of what genomic research results and secondary findings should be offered to a participant's family members, including after the participant's death. This is a pressing question for genomics projects involving participants with life-limiting diseases and projects archiving data for long-term research use. Balancing participant privacy and preferences regarding release of genomic data with family health and reproductive concerns is challenging. Data and policy guidance have been lacking on return to family in genomics research. Leveraging unique resources at the Mayo Clinic, University of Minnesota, and UCSF, this project is filling that gap.

Aim 1 has assessed individual and family member attitudes and preferences using in-depth qualitative interviews and a structured survey.[96] Aim 2 convened a multidisciplinary national working group to conduct an in-depth ELSI analysis of return of genomic results to family members, generating consensus recommendations published in *J Law Med Ethics* as part of a special issue produced by the project.[36, 97] We have

convened a national conference whose proceedings are archived online for free public access,[98] co-directed an international comparative workshop at the Brocher Foundation, and generated web-based resources, including an extensive bibliography. Aim 3 is prototyping and evaluating a procedure for offering probands' genomic results to family members. Aim 4 is developing tools for education on these issues, consent, and "best practice" governance by genomic biobanks.

Seattle Children's Hospital

The main goal of our project was to evaluate the use of a web-based tool, My46[99] for the management and return of secondary results from exome sequencing. We recruited 144 research participants or parents of minor research participants whose exomes were already sequenced as part of existing research studies on a range of Mendelian and complex phenotypes. Participants selected secondary result preferences using My46 by category: no primary results were offered for return. We offered a wide range of results for return, including results from the "ACMG list" and a range of secondary risk and carrier status results. Participants were randomized to receive results either by phone from a genetic counselor or through My46, with the option to talk to a genetic counselor after receiving results.

We assessed outcomes through online surveys (anxiety, depression, satisfaction, impact of results scales) and through interviews at three time points with a subset of participants. We evaluated use of My46, including result preference changing, reasons for preference changing, and site usage (e.g., review of educational material, time to set preferences and review results). We collected data about sharing of result information with family and health care providers. Analyses are ongoing, but suggest that there are no adverse impacts from use of My46 for return of results, when compared to return through a genetic counselor. We have published several papers on: 1) self-

guided management of CGES results,[100], 2) genetics professionals' attitudes towards return of CGES results[101] and 3) the practices and policies of existing ES clinical service providers.[102] Several manuscripts are in preparation about secondary results preferences, expectations and responses, parental decisions about secondary results for their children, and detailed comparison of endpoints between those receiving results from My46 and those receiving results from a genetic counselor.

Children's Mercy Hospital

This individual R21 project critically examines the conceptual and normative foundations of the claim that it is permissible, and perhaps even obligatory, to return certain individual research results in genomic research. It is, thus, philosophical in nature with an emphasis on clarifying important terms, concepts, and principles, drawing important distinctions, and analyzing and evaluating normative arguments related to ethical duties in genomic research. As such, the "results" of the research differ significantly in nature from standard empirical methodologies. That noted, in terms of measurable results, the project has thus far produced 5 publications in peer-reviewed medical and bioethics journals and 8 presentations at national meetings. The publications are as follows.[103-107]

Though funding for this project ended in August 2014, several journal articles remain under work with submission expected in the fall of 2015. These include a paper offering a historical and conceptual analysis of "actionability" as a fundamental criterion associated with the ethical duty to disclose individual research findings, as well as a paper examining how the purported right of children to an "open future" bears on ethical issues in pediatric genomics and pediatric genomic research (which will be presented and discussed within the CSER Pediatrics Working Group this fall).

Columbia University Medical Center

The aims of this study focused on the development of potential approaches for dealing with the key challenges regarding informed consent—especially for secondary findings—related to return of genomic data. Based on a systematic literature review, the investigators developed options for inclusion of information in the consent process, which were embodied in semi-structured interviews for genomic investigators (n=28) and research participants (n=20), and a survey for genomic researchers (n=254). (Interviews and survey were conducted jointly with the other Columbia R award described in this section.)

Ninety five percent of researchers surveyed believed that research participants should be offered secondary findings for highly penetrant disorders with immediate medical implications. However, there was no consensus on returning incidental results for other conditions. Regarding informed consent, most researchers and participants endorsed disclosure of extensive information about return of secondary findings. However, most researchers were willing to devote 30 minutes or less to this process.[108-110] Because of the disjunction between views about the information that should be disclosed and the time available, the findings strongly suggested a need for innovative approaches to informed consent. Based on the survey results and interviews, 4 models of consent were identified: traditional consent, staged consent, mandatory return, and outsourced consent.[111]

To ascertain how genomic investigators would respond to these models, we went back to our original subject pool. Responses from 198 genomic investigators indicated that, without resource constraints, approximately 1/3 would endorse either staged consent or traditional consent; outsourced consent and mandatory return were favored by only a small minority. However, taking resource constraints into account, roughly 50% would favor traditional consent, with support for staged consent only 13%. Thus,

traditional approaches are seen as most viable under current circumstances. However, there is considerable interest in staged consent, assuming the infrastructure to support it can be provided.[108]

Vanderbilt University

In our project, entitled "Returning Research Results of Pediatric Genomic Research to Participants," we proposed to focus primarily on the legal landscape in which these decisions are made. Put simply, our project could not have been more timely, given the enormous attention to pediatric genetic testing in recent years. Our group was quite productive, publishing four different papers that address legal and ethical issues in detail.[112-115] We have also contributed in important ways to the work of CSER regarding these issues.[7, 116, 117] Finally, several of us have been heavily engaged in discussions about pediatric genetic testing beyond the scope of this grant and the CSER Consortium in scholarly and in practical domains.

Supplemental Note: Focus and Progress of the CSER Working Groups

Electronic Health Records Working Group

This working group has a mission to "understand and facilitate cross site collaboration nationally around informatics work as related to a) integration into electronic health record (EHR), b) integration into decision support, and c) linkage to variant databases/knowledge bases (VDBKB). The group first focused on characterizing the current state of the art across the initial six CSER sites in terms of incorporating whole exome and genome sequencing data into the EHR for results review and for clinical decision support.[118] Key findings included heterogeneity in workflow and informatics tools with predominant mode of delivery of results being non-computable PDF documents with only two sites working on computerized decision support systems. Then in collaboration with the now eight CSER sites (the 9th not having an EHR) and eMERGE sites, the working group focused on identifying current approaches to the display of genetic information in the EHR (where in the record and how displayed) as well as making cross CSER/eMERGE recommendations for best practices.[31] Key findings included validating heterogeneity of information flow and importantly heterogeneity of results display even within a single institution depending on for example source of test results. Recommendations included improving consistency and interoperability among EHR systems that receive and display genetic information.[31] The working group is currently developing cross-institutional projects focused on genomic clinical decision implementation.[76]

Sequencing Standards Working Group

The mission of the Sequencing Standards working group is to develop a set of

technical standards for clinical sequencing, develop best practices for variant confirmation, and establish mechanisms for communicating uncertainty in clinical sequencing data. Key areas of focus include minimum coverage and quality metrics, turnaround time, data formats, and new approaches to sequence challenging genomic regions. The working group also helps establish tools to share sequence data between projects, and collaborates with other working groups and sites to share uniform quality standards. One of the main studies from the working group seeks to identify clinically relevant genomic regions that are poorly covered in whole genome and whole exome sequencing across all ten CSER sites. Briefly, the analysis of the working group identified poorly covered regions that are common to all sites, those that are dependent on specific methodology, and those that are unique to a single site. The study discusses factors that contribute to poorly covered regions, and examines the potential clinical impact of these poorly covered regions. In addition to highlighting clinically relevant poorly covered regions, the study provides a roadmap and tools for other sequencing centers to conduct similar analyses with their own data.

Genetic Counseling Working Group

This working group is investigating current genetic counseling topics related to clinical genome and exome sequencing (CGES), including but not limited to recruitment and enrollment, obtaining informed consent, returning sequencing results and interactions with patient participants and families in both research and clinical settings. The group has published the results of a qualitative interview study on experiences in informed consent for CGES.[3] These findings will contribute to the development of a guidance paper on informed consent in collaboration with the Informed Consent and Governance Working Group. In addition, the group has published case studies on challenging cases in informed consent and lessons learned in return of results.[4, 119]

Members of the working group have participated in the education of genetic counselors on the topic of informed consent at several national conferences including a plenary session at the National Society of Genetic Counselors (NSGC) Annual Education Conference in 2014. In addition, a two-part series was published in *Perspectives in Genetic Counseling*, a quarterly magazine published by the NSGC, on genetic counselors' roles within the CSER Consortium and balancing research and clinical roles.[120, 121] The group is in the planning stages for a second study analyzing experiences in return of results.

Actionability and Return of Results Working Group

This working group is defining the principles and processes guiding the definition of an "actionable" gene across the Consortium, highlighting common outcomes and seeking to understand the rationale underlying differences, to develop a consensus regarding the classification processes, and to develop resources to support decisions with respect to pathogenicity and actionability. The working group has published an in-depth report on the approach to secondary findings within each CSER project, the respective definitions of actionable genes, and examples of challenging cases,[70] as well as a collaborative paper with the eMERGE Consortium in which obligations and opportunities around the return of secondary results were further defined.[5] The working group is currently preparing a manuscript on best practices across the Consortium for variant sign out, as well as a manuscript summarizing the various CSER approaches to characterizing and returning recessive carrier traits, and undertaking initiatives around data sharing as well as the interface between clinical care and research.

Informed Consent Working Group

The Informed Consent & Governance (ICG) working group addresses the

pragmatics of the informed consent process and governance of genome sequencing by supporting the development of new and creative approaches to consent including standardized language and protocols; compiling CSER experiences with institutional governance of genomic data in research and clinical settings; and where appropriate, integrating governance recommendations with best practice and/or model language for consent. The working group has published a review of CSER project consent forms[90] and contributed to additional products led by the Pediatrics working group. The working group is currently preparing three manuscripts: one that provides guidance on consent for clinical sequencing, another commentary on the governance of returning results from genome sequencing, and a review of state disclosure laws and their impact on informed consent for CGES.

Outcomes and Measures Working Group

The goals of the Outcomes and Measures (OM) working group are to: (1) identify priority areas in psychosocial, behavioral, and outcomes research related to genome sequencing and return of results,[6] (2) facilitate the exchange of knowledge about psychosocial and behavioral outcome measurement across consortium projects, (3) develop research strategies to generate evidence that inform healthcare policies, and (4) develop new measures as needed. Early OM working group efforts centered on the coordination of measures across consortium sites for key outcomes such as anxiety, depression, multidimensional impact, and decision satisfaction. The OM working group is currently conducting preliminary cross-site analyses of psychosocial and healthcare resource utilization data in an effort to understand the heterogeneity of these outcomes across different populations and identify effective and pragmatic data collection approaches for future prospective studies. Additional ongoing projects include a cross-site investigation of participants' motivations for having sequencing and an evaluation of

the diverse range of qualitative methods used within the consortium research studies. The ultimate goal of the OM working group is to advance our understanding of the potential efficacy and harms of sequencing, as well as our understanding of the costs and impacts of genome sequencing on the healthcare system

Pediatrics Working Group

This working group seeks to (1) identify the unique ethical, legal, and practical challenges relating to clinical and translational genomics involving pediatric populations and (2) develop workable, appropriate solutions for addressing these challenges. The first product of the working group was a paper examining points of agreement and disagreement between two recommendation documents published in 2013,[7] the first issued jointly by the American Academy of Pediatrics (AAP) and American College of Medical Genetics and Genomics (ACMG) targeting genetic testing,[122] and the second issued by the ACMG focused on secondary genomic results.[22] A second product explores the responsibilities of parents and pediatric providers in making decisions related to genomic sequencing of children.[123]. A third paper, in press, proposes a framework for addressing consent for pediatric participants in genomic research as they reach the age of majority.[116] In the coming year, the working group is planning two projects: the first exploring how the concept of the child's right to an "open future" should be applied to pediatric genomic testing, and the second examining emerging methods used by investigators to keep pediatric research participants engaged with genomic research studies.

Tumor Working Group

The mission of the Tumor working group is to explore the unique technical, interpretive and ethical challenges and considerations involved in clinical tumor

sequencing and to contribute to the development of best practices for these tests. These collaborative efforts involve investigators from the three CSER sites performing clinical tumor sequencing as well as others focusing on germline studies of cancer phenotypes, given the critical shared challenges of tumor and germline sequencing. Working group efforts initially focused on education of the oncology community regarding the spectrum of potential results that can be revealed by clinical tumor and germline sequencing and their implications for laboratories, clinicians, and cancer patient participants. A manuscript on this topic related to the ACMG guidelines for reporting of germline secondary findings was published in the *Journal of Clinical Oncology* and a second manuscript focusing on the potential for discovery of clinically significant germline variants from tumor-only sequencing has recently been published in the Journal of the National Cancer Institute.[45, 124] Ongoing working group efforts have centered on annotation of tumor variants and the critical issue of determining "actionability". The working group and NIH staff organized a symposium on this topic at the 2015 AACR meeting and are currently partnering with the ClinGen Somatic working group to develop standards for tumor variant classification.

Practitioner Education

A core goal of the CSER Consortium is clinical implementation of genomics and there are a large number of practitioners participating in the ongoing trial. Given the accumulating experience with practitioner education within our consortium the CSER Steering Committee formed the Practitioner Education working group in Summer 2015 to explore the unique educational needs of healthcare providers. The term "practitioner" is broad and is meant to include physicians, nurses and other non-genetics specialist providers. We are currently compiling and assessing available resources and looking for gaps and avenues for using our expertise and shared experiences within CSER to help

practitioners better understand genomics and how to apply it in a clinical setting. Topics such as determining the most appropriate genetic test to order, how to interpret a genome sequence, dealing with uncertainty and discussing genomics with a patient/ patient participant will be important aspects to educational materials that are created and disseminated. Available educational resources for healthcare practitioners have been compiled and shared in a repository on the CSER Coordinating Center website.

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