Clinical Sequencing Exploratory Research Consortium

CSER Background Document in preparation for the

CSER and Beyond Meeting
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CSER: Introductions

Today, the availability of genomic sequencing for the public has outpaced the evidence base necessary to evaluate its effectiveness in clinical care. Like any new, important medical technology, it is imperative to understand the optimal implementation, advantages and limitations of genomic sequencing in the clinic before it is widely implemented in patient care. Premature implementation using sub-optimal strategies may lead to sub-optimal outcomes. Such an evidence base is also essential to insurers evaluating coverage of this new technology’s cost. Before whole exome and whole genome sequencing can become routine practice in patient care, many questions need to be answered, such as:

- How should clinical workflows, institutional policies, standard care procedures and electronic medical records evolve to accommodate genomic sequencing data? What best practices can be derived from a learning health-care system?
- What are the ethical, legal and psychosocial implications (ELSI) related to the use of genomic data? What do providers and/or patients need to optimally use this data? What fail-safes should be implemented to prevent errors, poor integration into care and poor outcomes?
- For what diseases does the addition of genomic sequencing significantly improve patient outcomes at reasonable cost? In what situations is genomic sequencing less impactful? What roles do individual gene and panel sequencing play?

To address these questions and other issues related to the use of genomic data in clinical care, the NHGRI initiated the Clinical Sequencing Exploratory Research (CSER) program. CSER is currently comprised of 18 primary research grants (see Appendix A), a coordinating center, a NIH intramural research project (ClinSeq) and other collaborators across the United States, spanning over 300 researchers, clinicians, bioethicists and more. CSER’s research includes both children and adults, in areas ranging from the diagnostic needs of children with developmental delay to adults with different forms of cancer, and explores sequencing across the lifespan, from pre-conception to late adulthood. Simultaneously, ethical issues related to these projects, such as the ELSI with the return of genomic sequencing results to children, adults and families, health economics and decision-making related to genomic results are also researched. CSER has diverse experimental approaches, cross-cutting working groups and covers a vast range of issues:

1. Technology: Generate and interpret genomic sequence data on patients in a variety of clinical contexts
2. Clinical Care: Study the challenges of integrating comprehensive, personal genomic sequence data to patient care
3. ELSI: Examine the ethical, psychosocial, and legal implications of bringing genomic sequence data into the clinic

The CSER Consortium seeks to rapidly advance the knowledge necessary to develop best practices for the implementation of genomic sequence data into clinical care. CSER is uniquely positioned among NHGRI programs to answer questions about the clinical implementation of genomic sequencing to meet its growing use in the clinical care of patients with diverse needs.

CSER at a Glance

- Funding: 9 U-grants and 1 Coordinating Center grant, $65M from FY11-F16 ($56.2M from NHGRI, $9.4M from NCI). $14.8M NHGRI funds in FY15
- “U-Grants” are described in RFAs HG-10-017, HG-12-010 and HG-12-015 to implement three integrated projects:
  1. Recruitment of patients and/or physicians in clinical settings to study genomic medicine implementation
  2. Generate and interpret genomic sequence data in a clinically useful format
  3. Ethical, legal, and psychosocial implications (ELSI) research
- “R-grants” are described in HG-11-003 and HG-11-004 and also explore ELSI issues related to the return of genomic results (originally funded as ELSI Return of Results Consortium)
- Over 200 publications and 700 presentations and posters to date, many high impact
- 9 Working Groups convened to identify and share common challenges and opportunities
- Identification of high priority cross-study projects, such as clinical exome coverage comparison, analysis of informed consent documents, best practices in variant sign-off, and variant pathogenicity annotation across sites
- Products from CSER work include a family pedigree app Proband (1700 downloads), a CSER variant database, 2617 ClinVar submissions, 1149 dbGAP submissions, and numerous other genomic tools like Atlas 2 and Cassandra
- Data analysis is currently underway and the most important quantitative study outcomes are in progress.
U-GRANTS: ACCOMPLISHMENTS AND OUTREACH

CSER’s U-Grant Sites, individually and collaboratively, have made significant advancements in researching the incorporation of genomic sequencing data into clinical care. This research has informed the development of best practices for genomic sequencing in the clinic, and has influenced communities and projects outside of CSER’s specific focus. These achievements include:

- Total enrollment of 4979 participants (3984 adults, 995 children)
- Collaborated with the eMERGE Network on a consensus statement on return of genomic research results and with other projects including Children’s Oncology Group, NSIGHT, ClinGen, IGNITE and the Undiagnosed Disease Network
- Variant interpretation “bake-offs” refined methodologies for the evaluating genomic variants to reduce discordant classification, and impacting care by influencing ACMG pathogenicity criteria
- Development of bioinformatics analysis tools, variant interpretation tools, patient facing information and other software used collaboratively by CSER projects and in the clinical services offered outside of CSER studies

NCGenes | University of North Carolina
- Discovered that effectiveness of WES varies with clinical presentation: retinal and neurological disorders demonstrate high diagnostic yields while standard clinical approach to familial cancer is less impacted by WES
- Collaborated with Vidant Cardiology (non-profit hospital system) to bring WES into a rural community with a large minority population
- Lessons learned include the need for geographically convenient clinics and offering accessible language resources for non-English speakers

“...through the pursuit of such collaborations that NCGenes accomplished one of its over-arching goals: robust minority participation (~25%)”

University of North Carolina

NEXT Medicine | University of Washington
- Determined the rate of actionable incidental findings and that the return of incidental findings and gene panels for colorectal cancer are cost-effective
- Extensive work on FDA regulation of genomic testing
- Worked with CERNER, EPIC and the Institute of Medicine to prioritize getting genomic information into the medical record in scalable, usable ways

“Our legal and regulatory analyses are widely cited for return of non-CLIA research results and also implications of new genomic medicine regulations.”

University of Washington

NEXTGen | Kaiser Foundation Research Institute
- Developed a framework for offering patient choice for results disclosure in the context of preconception carrier screening.
- Developed patient-facing materials, such as consent forms, clinical variant reports and educational materials that is shared with other CSER sites

“...consortium activities have enabled us to address questions that could not be answered by a single site.”

Kaiser Foundation Research Institute

MI-ONCOSEQ | University of Michigan
- Clinical sequencing of tumor samples identified actionable mutations in about 60% of patients, many of which aren’t routinely screened by standard diagnostic tests
- Developed “Onco1500,” a gene panel that targets 1500 genes to efficiently identify genetic aberrations in both highly recurrent cancer genes and additional candidate genes with suggestive links to cancer that expedites turnaround times.

“Some of the treating physicians have pursued therapies informed by sequence analysis, notably for pediatric patients”

University of Michigan

MedSeq | Brigham & Women’s Hospital
- Developed and refined a genomic medicine workflow, including iterative interaction between lab and clinic, for both diagnosis and prevention
- Completed pre-planned recruitment of randomized trial of sequencing measuring multi-modal medical, behavioral and economic outcomes
- Created a new method of complex blood serology typing through sequencing
- Contributed, through CSER interactions, to ACMG recommendations for NGS Laboratory Standards, Incidental Findings and Variant Classification

“Despite perceptions to the contrary, we are demonstrating that a pathway exists for physician preparedness to genomic medicine.”

Brigham & Women’s Hospital

ClinSeq | National Human Genome Research Institute
- Discovered it was practical and feasible to extract pathogenic variants from exome data for participants unselected for disease
- Contributed to ACMG recommendations for incidental findings that became the standard of care in genomic medicine

“Our work, and all of the CSER medical and genomic research is pointing to the same conclusion - genomics is just medicine”

NHGRI
CanSeq | Dana-Farber Cancer Institute

- Developed processes such as targeted sequencing and innovations such as methods for clinical analysis and interpretation of genomic information, and implemented these developments in Broad Institute’s CLIA Sequencing Lab
- Lessons from CanSeq have applied to projects in breast cancer, prostate cancer and other tumor types

BASIC3 | Baylor College of Medicine

- Preliminary research results suggested that exome results were most useful for oncologists when targeted treatment was available for the patient that was consistent with exome results
- Performed clinical exome sequencing of patients as they were diagnosed and disclosed results while patient is under treatment
- Participated in one-on-one consulting with major pediatric oncology institutions about starting their own clinical genome sequencing approaches

PediSeq | Children’s Hospital of Philadelphia

- Generated open-source software Proband, a family history pedigree app
- Created an Individualized Medical Genetics Center that influence approaches to genomic diagnostics clinically across all patients at CHOP
- Algorithms from preliminary investigations of clinical decision support by primary care physicians for incidental findings have been made applicable across non-genetic clinical workflows, such as care coordination

Hudson-Alpha Institute for Biotechnology

- Partnered with University of South Alabama and multiple regional clinics with the goal of using genomic sequencing in diagnosing children in underrepresented and underserved populations
- Data has been used to diagnose children with otherwise unexplained conditions and to get patients into appropriate specialty clinics

R-Grants: Achievements and Accomplishments

The introduction of new, important medical technology raises questions of the ethical, legal and psychosocial implications (ELSI) of its implementation. ELSI issues such as informed consent, return of results and methods of returning actionable incidental findings were researched. Nine R-Grant projects were initiated in parallel to the work done by the U-Grant sites to study ELSI issues.

Highlights of these R-Grant projects include:

- Developing legal and ethical frameworks if newborn screening will expand to use residual dried blood samples in genomic research (John Hopkins University)
- Investigating whether research participants want incidental findings returned and how participants respond to the return of incidental findings; develop a menu of approaches for informed consent for return of incidental findings (Columbia University)
- Studying the ethical and legal issues when returning genomic results to participants of pediatric research (Vanderbilt University)
- Ethical issues related to the implementation of large-scale mutation testing in the clinic (Mayo Clinic)
- Philosophical evaluation to critically analyze the moral obligation of researchers who study biorepository samples to return individual research results to participants (The Children’s Mercy Hospital)
- Whether or not participant preferences can reliably guide the return of research results (Boston Children’s Hospital)

“…preliminary analyses suggest there are no adverse reactions from use of My46 for return of results, when compared to return through a genetic counselor”

“…there is considerable interest in staged consent, assuming the infrastructure to support it can be provided.”

“we have learned a great deal about... providers’ willingness to encounter large-scale genomic data through the collective efforts of the CSER sites”

“nearly 40% of pediatric solid tumor patients have potentially actionable mutations when combining results of tumor and germline exome sequencing”

“We have collaborated with two other major pediatric centers based on knowledge gained from this project to extend our work in genomics”

“We have also shown that genomic testing can be done with minimal adjustments or alterations to current clinical workflows.”

Seattle Children’s Hospital

Columbia University

University of Minnesota
CSER Background Document: Metrics

**CSER Metrics**

**Total Enrollment**
As of September 2015, total enrollment is 4979 participants (1282 from ClinSeq). 3984 participants are adults and 995 participants are children.

![Total enrollment across time graph](image)

*Figure 1: Number of participants enrolled by CSER sites, including NHGRI ClinSeq (total = 4979)*

**Germline Sequencing Progress**
As of September 2015, 3989 participants had whole exome or whole genome sequencing completed (not all participants in CSER projects will receive sequencing). Of this number, 3047 participants are adults and 942 participants are children.

**September 2015: Germline Sequencing Progress**

![Adult Germline](image)

*Figure 2a: Number of adult participants who have had germline sequencing*

![Children Germline](image)

*Figure 2b: Number of child participants who have had germline sequencing*
Publications

As of September 2015, CSER Consortium membership has published over 200 publications, with at least 19 publications currently in press and has written many textbook chapters, op-eds, journal commentaries and online news articles. These publications have appeared in JAMA, NEJM, Genome Research, AJHG, Genetics in Medicine, Cell, and other numerous journals. See Appendix B for a selected list and Appendix C for a full list. Listed below is a selection of publications from CSER working groups.

Working Group Publications

Actionability & Return of Results (ROR)


Pediatrics


Electronic Health Records


Genetic Counsellors


Informed Consent and Governance


Outcomes and Measures


Presentations and Outreach

As of September 2015, CSER Consortium membership has given over 700 presentations and posters. CSER membership has presented at the ACMG, ASHG, ASBH, AACR, ASCO, PAS and NSGC, as well as at numerous other national and international meetings and conferences. Many presentations have occurred at large public events, such as TedMed and the Smithsonian Institute. Here is a small snapshot of the myriad of places where CSER membership has presented at:

- Beijing Genomics Institute; China, 2015
- Festival of Genomics; Boston 2015
- International Symposium on Genome Science; Japan, 2015 and 2013
- TedMed “There is no genome for the human spirit”; 2014
- Forbes Healthcare Summit; 2014;
- European Society of Human Genetics; Italy, 2014
- Cambridge Healthtech Institute’s Second Annual Advances in Prenatal Molecular Diagnostics Conference; Boston, 2014
- ScienceFriday Podcast, “Does your genome belong to your family, too?”; 2014
- International Rare Disease Research Symposium; China, 2014
- 26th Pezoller Symposium; Italy, 2014
- Human Genetics Organization (HUGO); Switzerland, 2014
- Israeli Society of Medical Genetics Annual Meeting; 2013
- Brocher Foundation Workshop “Returning Genetic Results in Biobanks: Opening an International Dialogue”; Switzerland, 2013
- Shanghai Jiao Tong University Seminar; China, 2013
- World Congress of Psychiatric Genetics; Boston, 2013
- PBS Radio and Television Documentaries
CSER: Future Opportunities

Selected opportunities where CSER can uniquely contribute to the field of genomic medicine are:

Clinical & Translational

- **Clinical diagnosis of unsolved cases.** Genome and exome sequencing currently solve approximately 25% of suspected genetic conditions. It is important for CSER 2.0 to improve diagnostic yield and explore the interface between clinical testing and discovery research by utilizing novel analysis (e.g., CNV analyses) of patients who had normal sequencing results in CSER 1.0.

- **Evaluation of downstream health and economic outcomes of clinical genome or exome sequencing.** CSER 2.0 would have the collective data across the funded sites that could serve as the foundation for continued development of evidence-based practices in the emerging area of clinical sequencing. This evidence base is needed to standardize care, give less experienced physicians a structure for best practices, and provide insurers and other health care reimbursement systems (payers) with the information they need to determine whether and under what circumstances their enrollees should have access to these genomic tests. Building upon current results, it will be critical to evaluate clinical outcomes along with comparative and cost effectiveness analyses.

- **Optimization of the delivery system to integrate genomic data into clinical workflows including 1) Best practices and scope of practice (workforce, licensing), 2) EHR integration, and 3) Insurance coverage.** Continuation of support through CSER 2.0 would demonstrate and guide how results are integrated into clinical care after they are received. This Consortium is prepared to tackle the refinement of clinical sequencing pipelines including: inter-operability of EMR systems, a focus on rapid turnaround time for urgent clinical scenarios (e.g., newborn in the NICU, unexplained heart failure, or tumor progression through initial treatment), automation of data sharing from labs to national databases, and establishing clinical decision support systems.

- **Investigation of the use of clinical sequencing within larger, more diverse populations.** The CSER research program would benefit from larger sample sizes, including a special focus on recruiting patients from diverse and underserved ancestry groups, more diverse regional and clinical settings, and healthy populations. Anticipation of population-scale clinical sequencing requires efforts to evaluate “healthy” populations and discovery of medically relevant variants in the absence of specific phenotypic indications. It is also important to expand access to genomic testing well beyond the confines of large academic medical centers in major population centers and to form partnerships.

- **Determination of appropriate use of genome and exome sequencing.** There is a need to understand how large-scale sequencing (either panel-based, exome or genome) are currently being used (or misused) in clinical settings and identify areas to innovate that optimize benefits and reduce unnecessary/inappropriate use.

- **Iterative phenotyping.** Sequencing provides an opportunity to perform hypothesis-generating research through iterative phenotyping. A key flaw in clinical genomics is incomplete phenotyping of patients studied for one specific indication. We suffer from a lack of a full understanding of the phenotypic spectrum of variants in the genes that are already associated with disease and the association of other genes with phenotypes may not be known. Current and future CSER cohorts could be utilized to deeply phenotype patients who are identified to have mutations in particular genes, including the use of longitudinal phenotyping and wearable sensors.

ELSI, Return of Results and Regulatory Efforts

- **Conduct biopsychosocial research.** Further biopsychosocial research is needed to ensure that the adoption of clinical sequencing tests takes place while maximizing benefits and mitigating harm to patients. Examples include improving the communication about the biopsychosocial dimensions of sequencing and supporting education and decision-making for both practitioners and patients during informed consent and when delivering results, especially uncertain test results.

- **Continue ELSI investigations.** The ethical, legal, and social implications of genetic testing will remain an important component of the CSER Consortium in the future. Legal and regulatory issues are particularly dynamic given FDA interest and changes to the Common Rule. Possible areas of research include 1) long term outcomes of testing in adolescents transitioning to adulthood, 2) testing new approaches (e.g., ways to give patients and clinicians choices of results) to support patient decision-making while minimizing bias, and 3) understand and impact legal ramifications of wide-spread genomic testing and the evolving regulatory climate.

- **Legal and Regulatory efforts.** With changes in the Common Rule and FDA regulation of genomic testing, CSER’s continued efforts to analyze, educate, and inform these changes are essential.
Appendix A: CSER Project Sites

APPENDIX A: CSER PROJECTS

A more detailed description of all CSER projects can be found on the CSER Consortium website.

CSER U-Grants

**BASIC**: Baylor College of Medicine | Sharon Plon & Will Parsons**
Examining the diagnostic yield, clinical utility and impact of whole exome sequencing (WES) on physicians and families of newly diagnosed pediatric cancer patients

**MedSeq**: Brigham & Women’s Hospital | Robert C. Green
Whole genome sequencing (WGS) targeting healthy adults from primary care and cardiomyopathy patients to evaluate WGS-derived information in patient care compared against current care standards

**PediSeq**: Children’s Hospital of Philadelphia | Ian Krantz & Nancy Spinner
WES in children with one of four conditions: intellectual disability, hearing loss, sudden cardiac arrest/death and mitochondrial disorders

**CanSeq**: Dana-Farber Cancer Institute | Levi Garraway & Pasi Jane
Introduction of WES into the care of lung and colorectal cancer

**NCGENES**: University of North Carolina | James P. Evans
Evaluating the diagnostic usefulness of WES in diverse clinical domains, such as dysmorphology, neurological disorders and familial cancer

**NEXT Medicine**: University of Washington | Gail Jarvik**
Investigating if WES can identify the genetic causes of colorectal cancer/polyps more often than usual clinic care

**Hudson-Alpha Institute for Biotechnology**: Greg Cooper &* Richard Myers*
Introducing WES into diagnostic needs of children with developmental delay and/or intellectual disability

**NEXTGen**: Kaiser Foundation Research Institute | Katrina Goddard & Benjamin Wilfond*
Introducing WGS into pre-conception carrier status testing for women and their partners

**MI-ONCOSEQ**: University of Michigan | Arul Chinnaiyan*
Application of high throughput sequencing towards precision cancer medicine

NIH Intramural Research

**ClinSeq**: National Human Genome Research Institute | Leslie Biesecker
WGS in health adults and adults with heart disease

CSER R-Grants

**Mayo Clinic**: Richard Sharp
Presenting diagnostic results from large-scale clinical mutation testing

**Columbia University**: Paul S. Appelbaum
Developing a menu of potential approaches to informed consent for the return of incidental findings

**Columbia University**: Wendy K. Chung
Impact of return of incidental genetic test results to research participants in the genomic era

**Children’s Hospital Boston**: Ingrid A. Holm
Returning research results in children: Parental Preferences and Expert Oversight

**Children’s Mercy Bioethics Center**: Jeremy R. Garrett
The presumptive case against returning individual results in biobanking research

**John Hopkins University**: Michelle Lewis
Return of research results from samples obtained for newborn screening

**University of California, San Francisco**, Mayo Clinic & University of Minnesota | Gloria Petersen, Barbara Koenig & Susan Wolf**
Disclosing incidental findings in a cancer biobank

**Seattle Children’s Hospital**: Holly K. Tabor
Innovative approaches to returning results in exome and genome sequencing studies

**Vanderbilt University**: Ellen Wright Clayton
Returning research results of pediatric genomic research to participants

Coordinating Center

**University of Washington**: Gail Jarvik, Debbie Nickerson, Wylie Burke & Peter Tarcyz-Hornoch*
The CSER Program’s Coordinating Center
Appendix B: Selected CSER Publications

Site-specific Publications

These are the three papers which the U-Grant sites deemed most impactful from their work:

CanSeq | Dana-Farber Cancer Institute

NEXT Medicine | University of Washington

MedSeq | Brigham & Women’s Hospital

NCGenes | University of North Carolina

PediSeq | Children’s Hospital of Philadelphia

Hudson-Alpha Intitute for Biotechnology
Appendix B: Selected CSER Publications

**ClinSeq | National Human Genome Research Institute**

**MI-ONCOSEQ | University of Michigan**

**BASIC3 | Baylor College of Medicine**

**NEXTGen | Kaiser Foundation Research Institute**
APPENDIX C: CSER Publications

The following list includes all peer-reviewed CSER publications, publications currently in press, along with textbook chapters, op-eds, online news articles, journal commentaries and other forms of publications.


Appendix C: CSER Publications


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209. Wright Clayton E. How much control do children and adolescents have over genomic testing, parental access to their results, and parental communication of those results to others? The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics (in-press). NIHMSID: 696583.

Appendix C: CSER Publications

220. Janssens ACJW, Evans JP. Returning pharmacogenetic secondary findings from genome sequencing: let’s not put the cart before the horse [Internet]. Genet Med 2015 May;