National Human Genome Research Institute

Clinical Sequencing Exploratory Research Program

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cser Clinical Sequencing Exploratory Research

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Abstract

The 2011 National Human Genome Research Institute (NHGRI) Strategic Plan recognized the potential benefits to patients of comprehensive genomic data that soon will be available to clinicians with the rapid deployment of new DNA sequencing instruments and methods. NHGRI subsequently crafted the Clinical Sequencing Exploratory Research (CSER) initiative to: 1) leverage NHGRI's long-standing experience in genomic sequencing and analysis to ease the adoption of these methods into clinical care, 2) guide the development and dissemination of best practices for the integration of clinical sequencing into clinical care, and 3) research the ethical, legal, and psychosocial implications of bringing broad genomic data into clinical decision-making. The CSER Consortium is currently composed of nine multi-disciplinary projects (six awarded in 2011 and three added in 2013; three are co-funded by NCI), nine Ethical, Legal, and Social Implications (ELSI)-specific projects which formerly comprised the Return of Results Consortium (one is NCI-cofunded), and a Coordinating Center. Members of NHGRI's Intramural ClinSeq program also participate. Aims of the research include: generating and interpreting genomic sequence data on patients in a variety of clinical contexts; outlining the principles and processes guiding the definition and reporting of an 'actionable' variant across the Consortium; and exploring standardized approaches to addressing the unique ELSI challenges related to generating sequence information in clinical settings. The Consortium of grantees will cooperate to generate a knowledge base to advance best practices and communicate lessons learned to the community. The organization of the Consortium across study sites and Working Groups, Consortium progress to date, anticipated products and results, and the Consortium's role in broader efforts at NHGRI relating to genomic medicine will be described.

http://www.genome.gov/cser
https://cser-consortium.org/

Program Goals

1. Identify and characterize the challenges to applying genomic sequencing data to clinical care, including:
   - Generate and apply genomic sequence data in the clinical workflow
   - Interpret and translate data for the physician
   - Communicate to the patient
2. Examine the ethical, legal, and psychosocial implications of clinical genomics

Members

	Institution	Clinical focus
U-grants (2011)	Baylor College of Medicine*	Childhood cancer patients
	Brigham and Women's Hospital	Primary care patients, cardiomyopathy patients
	Children's Hospital of Philadelphia	Pediatric patients with one of four conditions: intellectual disability; sudden cardiac arrest; hearing loss; mitochondiral disorders
	Dana-Farber Cancer Institute / Broad Institute	Patients with advanced lung and colorectal cancer
	University of North Carolina	Patients from one of five clinical domains: cancer; cardiology; dysmorphology; neurodevelopmental; ophthalmology
	University of Washington*	Patients undergoing colorectal cancer genetic testing
U-grants (2013)	Hudson-Alpha Institute for Biotechnology	Children with intellectual disability and/or developmental delay
	Kaiser Foundation Research Institute	Women and their partners seeking pre-conception carrier testing
	University of Michigan*	Patients with advanced sarcoma or other rare cancers
	University of Washington (CC)	Facilitates the scientific work of the CSER consortium
NIH	NHGRI ClinSeq	Healthy adults and adults with heart disease

	Institution	Study Title
R01 and R21 Grants (Return of Results)	Mayo Clinic	Presenting diagnostic results from large-scale clinical mutation testing
	Columbia University (Appelbaum)	Challenges of informed consent in return of data from genomic research
	Columbia University (Chung)	Impact of return of incidental genetic test results to research participants in the genomic era
	Children's Hospital Boston	Returning research results in children: Parental Preferences and Expert Oversight
	Children's Mercy Bioethics Center	The presumptive case against returning individual results in biobanking research
	Johns Hopkins University	Return of research results from samples obtained for newborn screening
	University of California, San Francisco*	Disclosing genomic incidental findings in a cancer biobank: An ELSI experiment
	Seattle Children's Hospital	Innovative Approaches to Returning Results in Exome and Genome Sequencing Studies
	Vanderbilt University	Returning research results of pediatric genomic research to participants

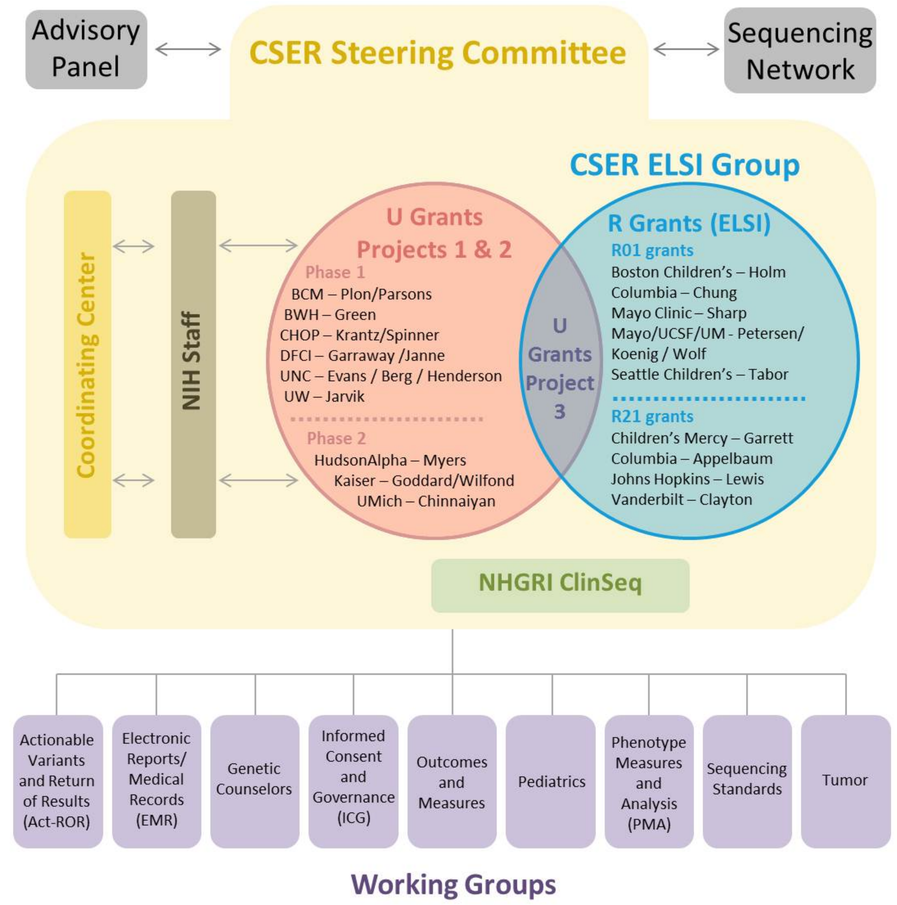
- * Co-funded by National Cancer Institute
- "U-grants" are described in RFAs HG-10-017, HG-12-010, and HG-12-015 and implement three integrated projects: 1) recruitment of patients and physicians in a clinical setting; 2) generation and interpretation of genomic sequence data in a clinically useful format; 3) ethical, legal, and psychosocial research
- "R-grants" are described in HG-11-003 and HG-11-004 and explore a broad range of ethical, legal, and psychosocial issues related to return of genomic results (originally funded as ELSI Return of Results Consortium)

Working Groups

Group Name (Chairs)	Key Opportunities	Focus of Upcoming Papers and Products
Actionable Variants and Return of Results Laura Amendola, Wendy Chung	• Principles and case studies guiding identification of 'actionable' genes • Consensus regarding the classification process of identified variants in actionable genes; resources to support decisions • Best practices for returning genomic findings to the patient	• Site-specific lists of 'Bin 1' genes • Joint database of juried variants • Consensus on reporting formats
Electronic Reports/ Medical Records Brian Shirts	• Variant annotation, prioritization, integration into electronic medical record, and integration into decision support	• Informatics approaches to whole exome or whole genome clinical reporting in the electronic medical record
Genetic Counselors Denise Lautenbach, Sarah Scollon	• Collaborations between projects and consortia (CERC, eMERGE) to share knowledge, approaches to returning results and informed consent, lessons from troubleshooting, etc.	• Analysis of genetic counselors' informed consent experiences across sites to inform best practices • Educational materials for primary providers
Informed Consent & Governance Paul Appelbaum, Joon-Ho Yu	• Approaches to informed consent in the context of clinical sequencing • Standardized consent language and protocols • Experiences with institutional governance of genomic data and integration of recommendations with model language for informed consent	• Consent practices/documents and governance models
Pediatrics Kyle Brothers, Benjamin Wilfond	• Ethical, legal, and practical challenges relating to returning results in studies involving pediatric populations.	• Pediatric issues in genomics • Decision-making authority in pediatric ethics
Phenotype Measures and Analysis Matt Deardorff	• Approaches to genome-phenotype analysis and evaluation of factors limiting in-depth phenotype measure collection • Common phenotypic measures that can be applied to enable integrating subject descriptive data across studies	• Phenotype measures and tools across sites • Minimal set of phenotypes potentially useful for clinical sequencing
Sequencing Standards Nick Wagle, Donna Muzny	• Technical standards for sequencing in a clinical context • Best practices for variant validation • Current practices and new approaches to cover difficult regions	• Meta analysis of data, metrics, etc. using cross-site sequencing data and incorporating "mission-critical genes" • Analytical approaches and validation methods
Tumor Will Parsons	• Approaches to somatic and germline analysis in clinical sequencing of cancer genomes • Best practices for clinical sequencing of cancer genomes	• Germline reporting in clinical tumor sequencing • Tumor-only next-generation sequencing implications

Selected Accomplishments

- Established clinical sequencing pipelines and variant annotation/interpretation resources for germline and somatic samples
- Generated publically available software tools or databases (e.g., TARGET, PHIAL, Proband, Varify, Atlas)
- Disseminated physician educational materials for non-geneticists
- Constructed a widely disseminated list of gene-disease pairs that are actionable in adults and estimated the rate of such incidental findings from 2000 exomes
- To date, the CSER Consortium has published over 100 manuscripts



Recent CSER Manuscripts

Am J Hum Genet. 2014 Jun 5;94(6):818-26. doi: 10.1016/j.ajhg.2014.04.009. Epub 2014 May 8.
Return of genomic results to research participants: the floor, the ceiling, and the choices in between.
Jarvik GP[1], Amendola LM[2], Berg JS[3], Brothers K[4], Clayton EW[5], Chung W[6], Evans BJ[7], Evans JP[3], Fullerton SM[8], Gallego CJ[2], Garrison NA[5], Gray SW[9], Holm IA[10], Kullo IJ[11], Lehmann LS[12], McCarty C[13], Prows CA[14], Rehm HL[12], Sharp RR[15], Salama J[2], Sanderson S[16], Van Driest SL[5], Williams MS[17], Wolf SM[18], Wolf WA[19], eMERGE Act-ROR Committee and CERC Committee; CSER Act-ROR Working Group, Burke W[8].

Genet Med. 2013 Nov;15(11):860-7. doi: 10.1038/gim.2013.133. Epub 2013 Oct 24.
Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium.
Berg JS[1], Amendola LM, Eng C, Van Allen E, Gray SW, Wagle N, Rehm HL, DeChene ET, Dulik MC, Hisama FM, Burke W, Spinner NB, Garraway L, Green RC, Plon S, Evans JP, Jarvik GP; Members of the CSER Actionability and Return of Results Working Group.

Genet Med. 2014 Mar 13. doi: 10.1038/gim.2014.26. [Epub ahead of print]
Social and behavioral research in genomic sequencing: approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group.
Gray SW[1], Martins Y[2], Feuerman LZ[3], Bernhardt BA[4], Biesecker BB[5], Christensen KD[6], Joffe S[7], Rini C[8], Veenstra D[9], McGuire AL[3].

Am J Bioeth. 2014 Mar;14(3):3-9. doi: 10.1080/15265161.2013.879945.
Addressing the ethical challenges in genetic testing and sequencing of children.
Clayton EW[1], McCullough LB, Biesecker LG, Joffe S, Ross LF, Wolf SM, For The Clinical Sequencing Exploratory Research Cser Consortium Pediatrics Working Group.

Genet Med. 2013 Oct;15(10):824-32. doi: 10.1038/gim.2013.120. Epub 2013 Sep 26.
A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record.
Tarczy-Hornoch P[1], Amendola L, Aronson SJ, Garraway L, Gray S, Grundmeier RW, Hindorff LA, Jarvik G, Karavite D, Lebo M, Plon SE, Van Allen E, Weck KE, White PS, Yang Y.