

# Clinical Sequencing Exploratory Research Program

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Division of Medicine  
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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 the Institute'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), nine Ethical, Legal, and Social Implications (ELSI)-specific projects (which formerly comprised the Return of Results Consortium), and a Coordinating Center. Aims of the research include: generating genomic sequence data on patients in a variety of clinical contexts; outlining the principles and processes guiding the definition of an 'actionable' variant across the Consortium; and exploring standardized approaches to addressing the unique ELSI challenges relating to returning results in studies involving both adult and pediatric populations. The Consortium of grantees will cooperate to evaluate best practices in this rapidly advancing field and communicate these to the community. The organization of the Consortium across study sites and Working Groups, 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/27546194>

<https://cser-consortium.org/>



## PROGRAM GOALS

1. Identify and characterize the challenges to applying comprehensive genomic sequence data to the care of patients:
  - Generation and application of genomic sequence data in the clinical workflow and timeline
  - Interpretation and translation of the data for the physician
  - Communication to the patient
2. Examine the ethical, legal, and psychosocial implications of bringing broad genomic data into the clinic.

## GRANTEES

	Institution	Principal Investigator(s)	Clinical focus
Funded in 2011	Baylor College of Medicine* Houston, TX	Sharon Plon D. Will Parsons	Childhood cancer patients with high-risk solid tumors and brain tumors
	Brigham and Women's Hospital Boston, MA	Robert C. Green	Primary care patients, cardiomyopathy patients
	Children's Hospital of Philadelphia Philadelphia, PA	Ian Krantz Nancy Spinner	Pediatric patients with one of four conditions - intellectual disability, sudden cardiac arrest/death, hearing loss, and mitochondrial disorders
	Dana-Farber Cancer Institute / Broad Institute Boston, MA	Levi Garraway Pasi Janne	Patients with advanced lung and colorectal cancer
	University of North Carolina Chapel Hill, NC	James P. Evans	Patients from one of five clinical domains - cancer, cardiology, dysmorphology, neurodevelopmental and ophthalmology
	University of Washington* Seattle, WA	Gail Jarvik	Patients who have clinical indications for colorectal cancer/polyposis (CRCP) genetic testing
Funded in 2013	Hudson-Alpha Institute for Biotechnology Huntsville, AL	Richard Myers	Children with intellectual disability and/or developmental delay
	Kaiser Foundation Research Institute Oakland, CA	Katrina Goddard Benjamin Wilfond	Women and their partners seeking pre-conception carrier testing
	University of Michigan* Ann Arbor, MI	Arul Chinnaiyan	Patients with advanced sarcoma or other rare cancers
	University of Washington Seattle, WA (Coordinating Center)	Gail Jarvik	Facilitates the scientific work of the CSER consortium and its working groups by providing logistical and scientific expertise; disseminates findings and approaches to the biomedical research community
Formerly the Return of Results Consortium	Institution	Principal Investigator	Study Title
	Mayo Clinic Rochester, MN	Richard Sharp	Presenting diagnostic results from large-scale clinical mutation testing
	Columbia University New York City, NY	Paul S. Appelbaum	Challenges of informed consent in return of data from genomic research
	Columbia University New York City, NY	Wendy K. Chung	Impact of return of incidental genetic test results to research participants in the genomic era
	Children's Hospital Boston Boston, MA	Ingrid A. Holm	Returning research results in children: Parental Preferences and Expert Oversight
	Children's Mercy Bioethics Center Kansas City, MO	Jeremy R. Garrett	The presumptive case against returning individual results in biobanking research
	Johns Hopkins University Baltimore, MD	Michelle Huckaby Lewis	Return of research results from samples obtained for newborn screening
	University of California, San Francisco* San Francisco, CA	Barbara Koenig	Disclosing genomic incidental findings in a cancer biobank: An ELSI experiment
	University of Washington Seattle, WA	Holly K. Tabor	Innovative Approaches to Returning Results in Exome and Genome Sequencing Studies
	Vanderbilt University Nashville, TN	Ellen Wright Clayton	Returning research results of pediatric genomic research to participants

\* Co-funded by National Cancer Institute

## WORKING GROUPS

Group Name (Chairs)	Key Opportunities	Focus of Upcoming Papers and Products
Actionable Variants and Return of Results Laura Amendola, Wendy Chung	<ul style="list-style-type: none"> <li>• Principles and case studies guiding identification of 'actionable' genes</li> <li>• Consensus regarding the classification process of identified variants in actionable genes; resources to support decisions</li> <li>• Best practices for returning genomic findings to the patient</li> </ul>	<ol style="list-style-type: none"> <li>1. Site-specific lists of 'Bin 1' genes</li> <li>2. Joint database of juried variants</li> <li>3. Consensus on reporting formats</li> </ol>
Analysis and Phenotype Measures Ian Krantz, Peter White	<ul style="list-style-type: none"> <li>• Inventory of clinical outcomes to maximize cross-study sample sizes</li> <li>• Approaches to genotype-phenotype analysis</li> </ul>	<ol style="list-style-type: none"> <li>1. Phenotype measures and tools across sites</li> <li>2. Minimal set of phenotypes potentially useful for clinical sequencing</li> </ol>
Electronic Reports/ Medical Records Peter Tarczy-Hornoch	<ul style="list-style-type: none"> <li>• Variant annotation, prioritization, integration into electronic medical record, and integration into decision support</li> </ul>	Informatics approaches to whole exome or whole genome clinical reporting in the electronic medical record
Genetic Counselors Denise Lautenbach, Sarah Scollon	<ul style="list-style-type: none"> <li>• Collaborations between projects and consortia (CERC, eMERGE) to share knowledge, approaches to returning results and informed consent, lessons from troubleshooting, etc.</li> </ul>	<ol style="list-style-type: none"> <li>1. Analysis of genetic counselors' informed consent experiences across sites to inform best practices</li> <li>2. Educational materials for primary providers</li> </ol>
Informed Consent & Governance Paul Appelbaum, Joon-Hu Yu	<ul style="list-style-type: none"> <li>• Approaches to informed consent in the context of clinical sequencing</li> <li>• Standardized consent language and protocols</li> <li>• Experiences with institutional governance of genomic data and integration of recommendations with model language for informed consent</li> </ul>	Consent practices/documents and governance models
Outcomes and Measures Gail Henderson, Amy McGuire	<ul style="list-style-type: none"> <li>• Instruments to measure psychosocial outcomes related to returning results</li> </ul>	<ol style="list-style-type: none"> <li>1. Database of shared resources related to outcomes measures</li> <li>2. Domains of interest and coordinated outcomes in each of the major domains</li> </ol>
Pediatrics Ellen Clayton, Laurence McCullough	<ul style="list-style-type: none"> <li>• Ethical, legal, and practical challenges relating to returning results in studies involving pediatric populations.</li> </ul>	<ol style="list-style-type: none"> <li>1. Pediatric issues in genomics</li> <li>2. Decision-making authority in pediatric ethics</li> </ol>
Sequencing Standards Levi Garraway	<ul style="list-style-type: none"> <li>• Technical standards for sequencing in a clinical context</li> <li>• Best practices for variant validation</li> <li>• Current practices and new approaches to cover difficult regions</li> </ul>	<ol style="list-style-type: none"> <li>1. Meta analysis of data, metrics, etc. using cross-site sequencing data and incorporating "mission-critical genes"</li> <li>2. Analytical approaches and validation methods</li> </ol>

## NHGRI GENOMIC MEDICINE PROGRAMS

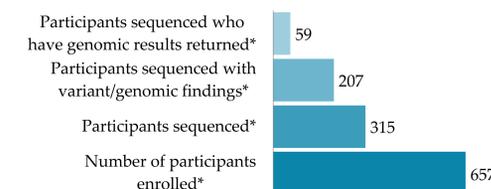
	CSER	ClinGen	eMERGE	IGNITE	NBS
Variant/ Association Discovery	+		++		+
Evidence Generation	++		++	++	++
Clinical Implications of Genomic Variants	++	++	++	+	++
Informed Consent Concerns	++		++	+	++
Variant Reporting and Use in Care	++		+	+	++
Clinician/ Patient Education	++	+	++	+	++
Tools for Decision Support	+		+	+	+
Policy Development	++		+	+	+

CSER: Clinical Sequencing Exploratory Research; ClinGen: Clinical Genome Resource; eMERGE: Electronic Medical Records and Genomics; IGNITE: Implementing Genomics into Clinical Practice Network; NBS: Newborn Sequencing U19s

+ = minor focus  
++ = major focus

## STATUS OF RESEARCH AND POTENTIAL IMPACT

- Sites use a range of approaches to returning incidental findings and some allow patients to opt out of medically actionable (or not) findings.
- Sites use a range of approaches to determining actionability ranging from a case by case basis to an *a priori* categorization of actionable genes (including the ACMG recommendations)
- 34.7% of the enrolled participants are children\* (under 18)



### Research support statistics\*

Clinicians	200
Non-clinical researchers	177
Publications	39
Presentations and posters	40

\* as of September 2013

- Best practices and lessons learned will contribute to Advancing the Science of Medicine (NHGRI Strategic Plan - Area 4)

