Clinical Sequencing Exploratory Research (CSER)

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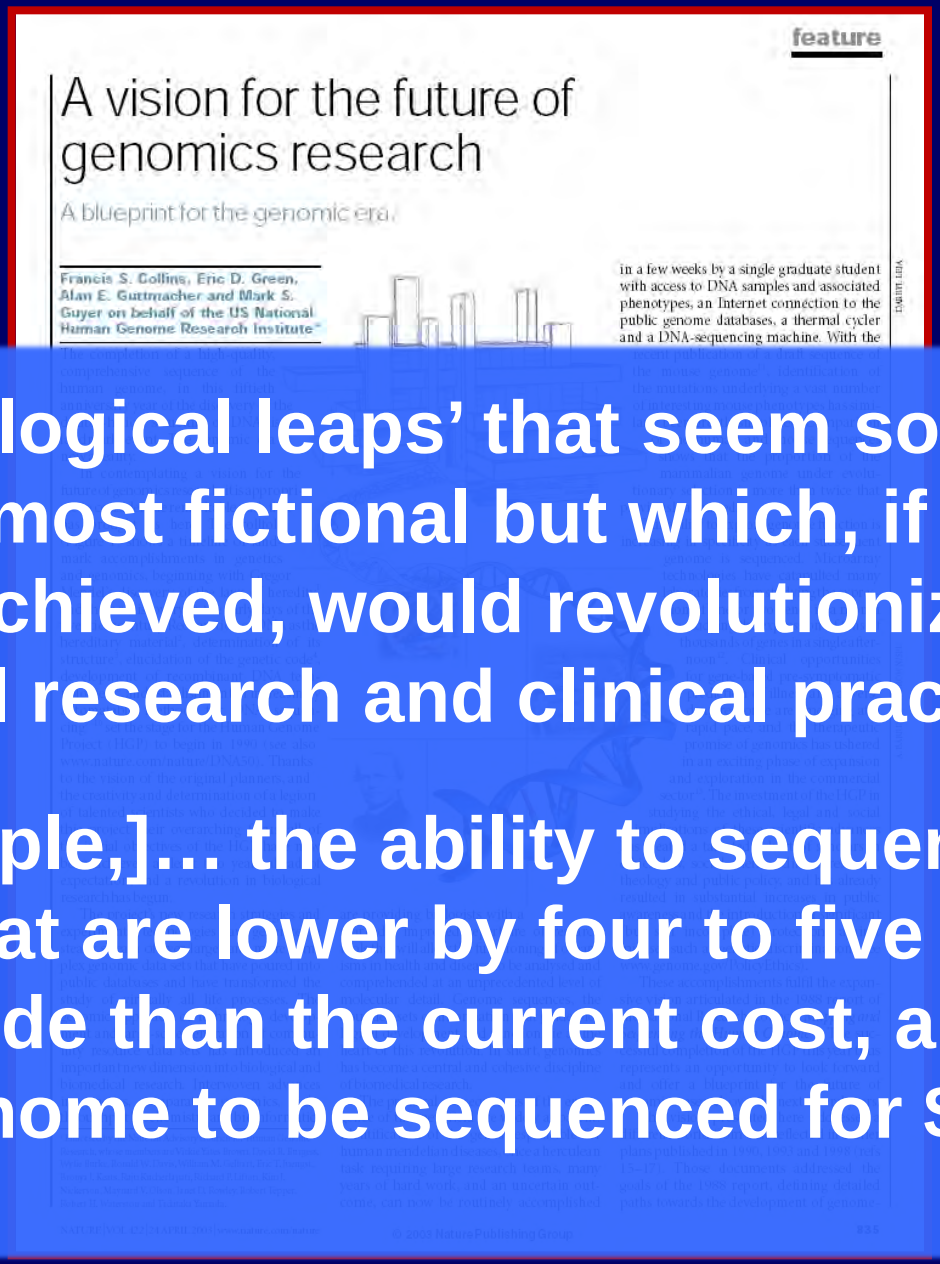
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A vision for the future of genomics research

A blueprint for the genomic era

Francis S. Collins, Eric D. Green, Alan E. Guttmacher and Mark S. Guyer on behalf of the US National Human Genome Research Institute*

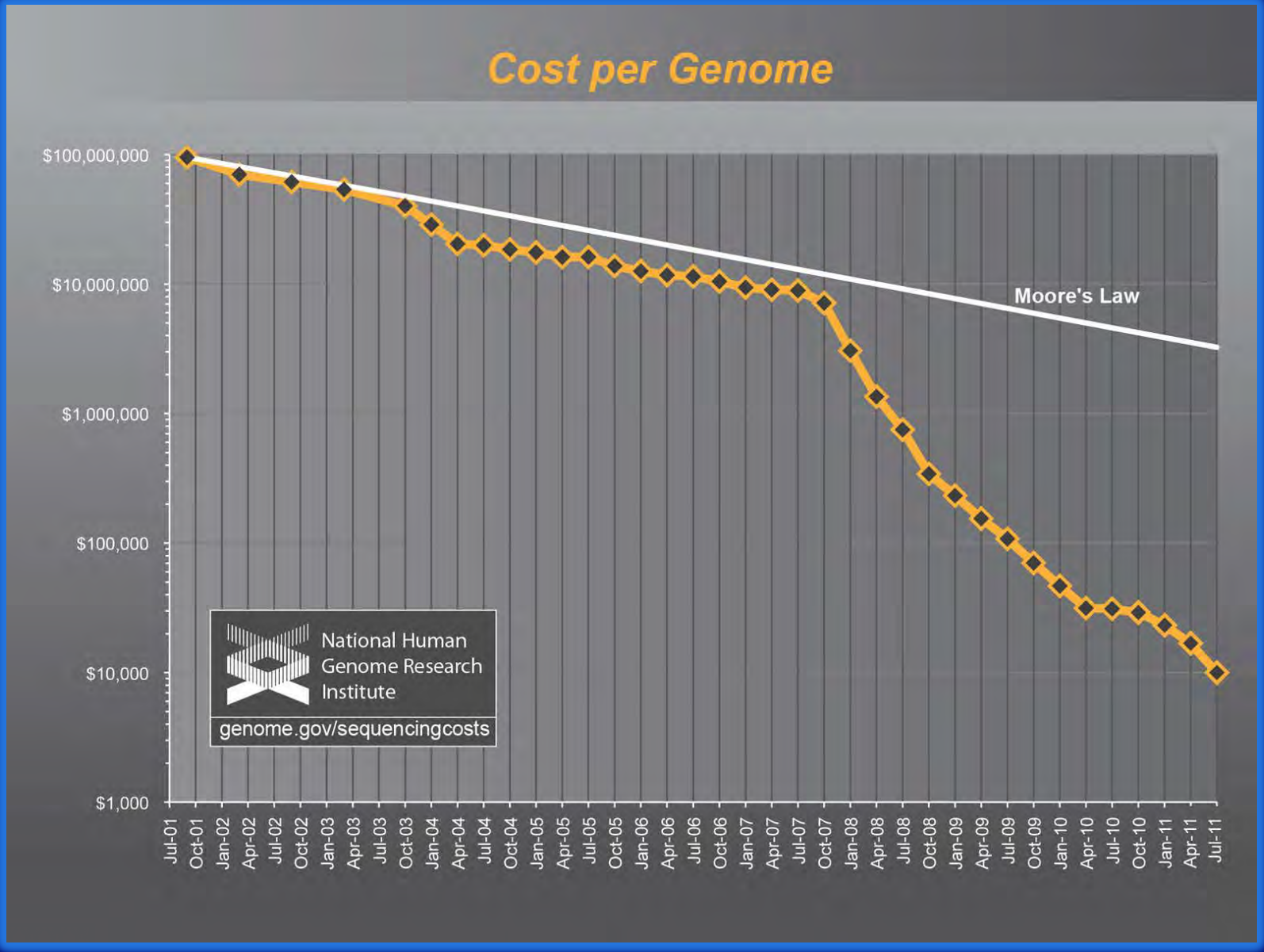
in a few weeks by a single graduate student with access to DNA samples and associated phenotypes, an Internet connection to the public genome databases, a thermal cycler and a DNA-sequencing machine. With the

"…'technological leaps' that seem so far off as to be almost fictional but which, if they could be achieved, would revolutionize biomedical research and clinical practice.

[For example,]… the ability to sequence DNA at costs that are lower by four to five orders of magnitude than the current cost, allowing a human genome to be sequenced for $1,000 or less."

***Nature*, April 2003**

Cost per Sequenced Human Genome



And Yet Newer Technologies…

The Path to Genomic Medicine

Routine Genome Sequencing

Human Genome Project

Realization of Genomic Medicine

The Largest Current Bottleneck in Genomics…


4 September 2008 | www.nature.com/nature | $10
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
nature
THE BITER BIT
Viral infections for viruses
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SCIENCE IN THE PETABYTE ERA


11 February 2011 | $10
Science
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Big Data to Knowledge (BD2K): Overview

- **Trans-NIH effort with the overarching goal of:**

  By the end of the decade, enable a quantum leap in the ability of the research community to maximize the value of the growing volume and complexity of biomedical data

- **Strong support across NIH**

  - **Working group has about 125 members**
  - **Staff from 24 Institutes/Centers and several other offices involved**

BD2K: Four Programmatic Areas

I. Facilitating Broad Use of Biomedical Big Data

II. Developing and Disseminating Analysis Methods and Software for Biomedical Big Data

III. Enhancing Training for Biomedical Big Data

IV. Establishing Centers of Excellence for Biomedical Big Data

BD2K: Update

- **Timeline:**

  Series of workshops, beginning this summer

  > Enabling Research Use of Clinical Data, Sept. 2013

  Funding starts in Fiscal Year 2014

- **Funding**

FY14	FY15	FY16
$27M	$80M	$99M

GENOMICS

Sequencing set to alter clinical landscape

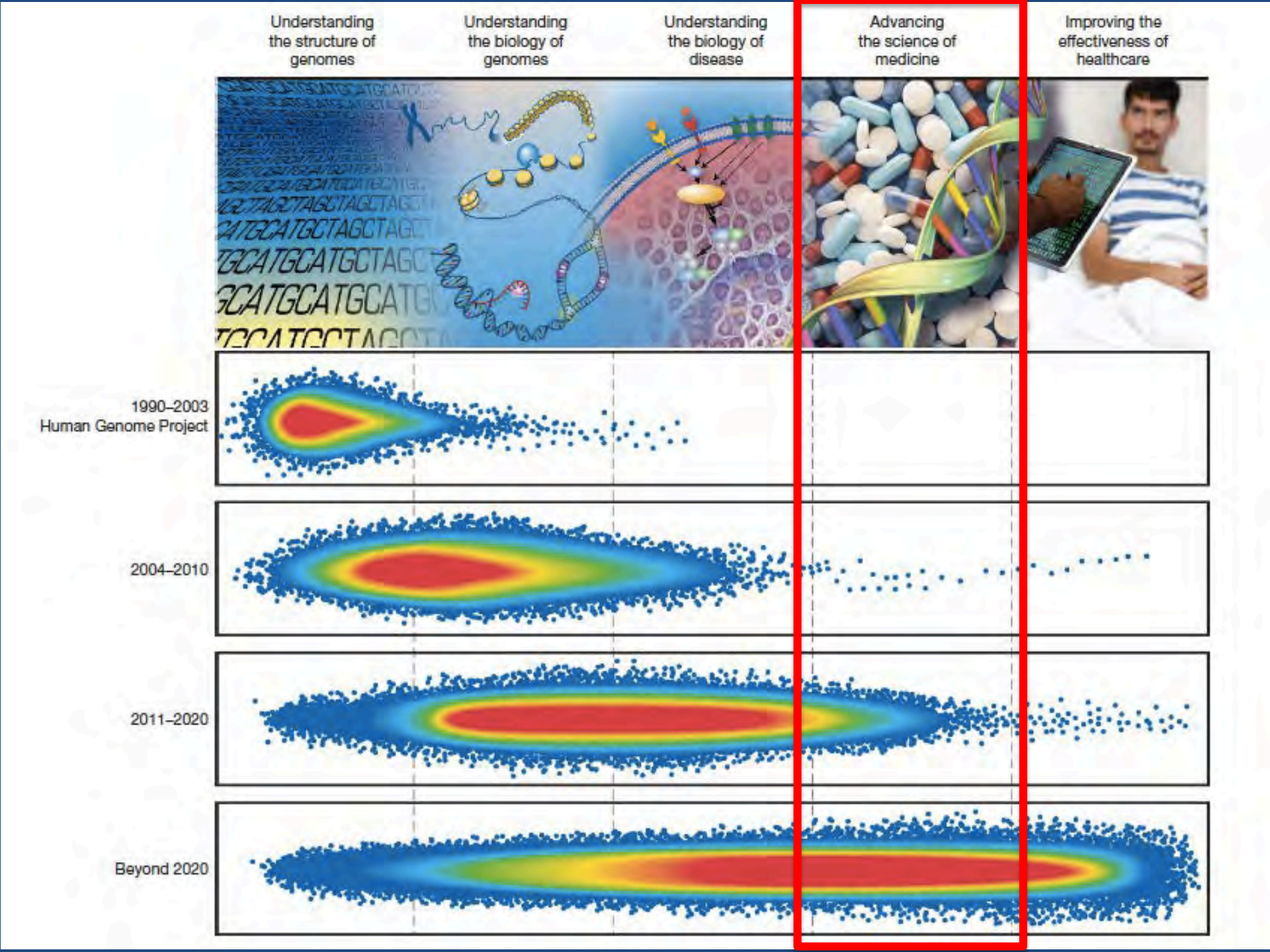
Access to whole genomes shifts potential for diagnosis, but poses challenges for doctors and regulators.

***Nature* (2012)**

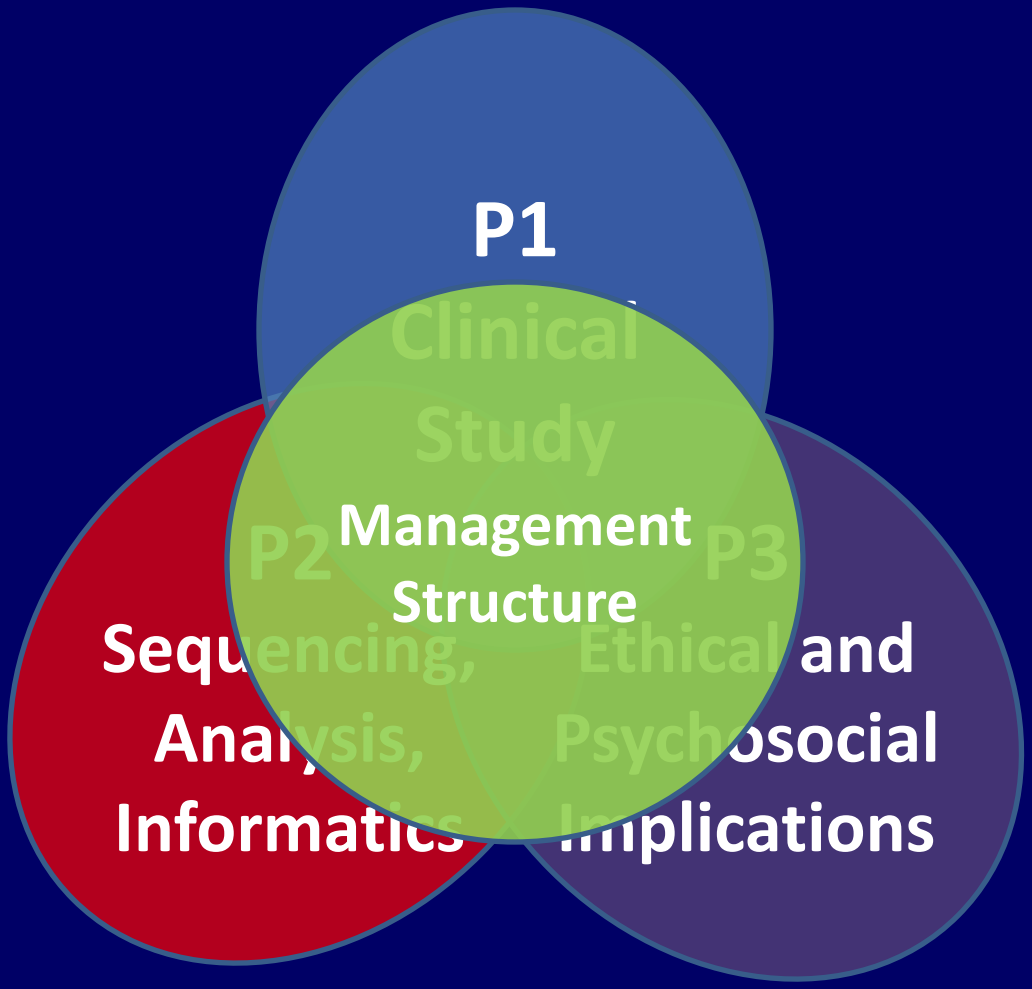
RFA HG 10 -017, HG 12-009

Clinical Sequencing Exploratory Research

- Research 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.
- Examine the ethical and psychosocial implications of bringing broad genomic data into the clinic.


Understanding the structure of genomes
Understanding the biology of genomes
Understanding the biology of disease
Advancing the science of medicine
Improving the effectiveness of healthcare
1990–2003 Human Genome Project
2004–2010
2011–2020
Beyond 2020

CSER Project Structure



Clinical Sequencing Exploratory Research (CSER) Consortium

Institution	PI (ELSI lead)	Title
U. North Carolina	Evans (Henderson)	North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing
Dana Farber Cancer Institute	Garraway (Joffe)	The Use of Whole-Exome Sequencing to Guide the Care of Cancer Patients
Brigham and Women's Hospital	Green (McGuire)	Integration of Whole Genome Sequencing into Clinical Medicine
University of Washington*	Jarvik (Burke, Fullerton)	Clinical sequencing in cancer: Clinical, ethical, and technological studies
Children's Hospital of Philadelphia	Krantz, Spinner (Bernhardt)	Applying Genomic Sequencing in Pediatrics
Baylor College of Medicine*	Plon, Parsons (McCullough, Street)	Incorporation of Genomic Sequencing into Pediatric Cancer Care

***co-funded by NCI**

From G. Jarvik

Return of Results (ROR) Consortium

Institution	PI	Title
Columbia University	Chung, Phelan	Impact of return of incidental genetic test results to research participants…
Boston Children's Hospital	Holm	Returning research results in children: Parental preferences and expert oversight
Seattle Children's Hospital/U. Wash.	Tabor, Bamshad	Innovative approaches to returning results in exome and genome sequencing studies
Columbia University	Appelbaum	Challenges of informed consent in return of data from genomic research
Vanderbilt University	Clayton, Mc-Guire, Knoppers	Returning research results of pediatric genomic research to participants
The Children's Mercy Hospital	Garrett	The presumptive case against returning individual results in biobanking research
Johns Hopkins University	Huckaby Lewis	Return of research results from samples obtained for newborn screening

From G. Jarvik

Working Groups

Group	Chair(s)	Consortium
Phenotype Measures & Analysis	Ian Krantz	CSER
Sequencing Standards	Levi Garraway	CSER
Actionability & Return of Results	Gail Jarvik & Jonathan Berg	CSER
Electronic Medical Records	Peter Tarczy-Hornoch	CSER
Psychosocial Measures & Instruments	Amy McGuire	CSER & ROR
Informed Consent & Governance	Paul Applebaum & Malia Fullerton	CSER & ROR
Pediatrics	Ellen Clayton & Larry McCullough	CSER & ROR
EMPIROR	Robert Green & Richard Sharp	ROR

Clinical Sequencing Exploratory Research (CSER) Projects

Measuring progress / considering objectives

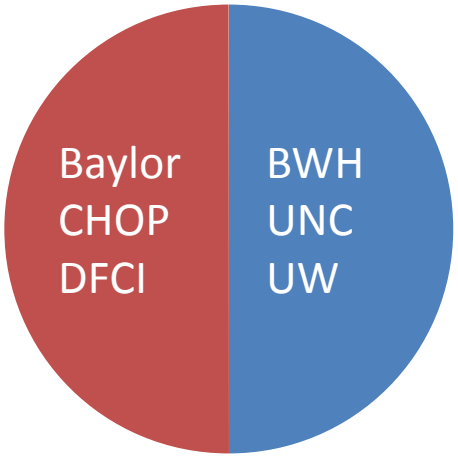
- CSER Consortium recruitment of participants

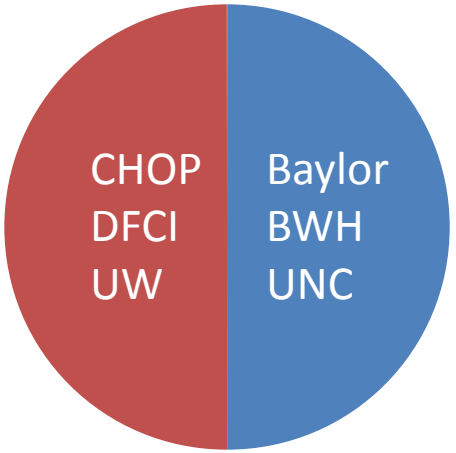
Patients/Participants			Physicians
Contacted	Consented	Sequenced	Enrolled
781	455	170	95

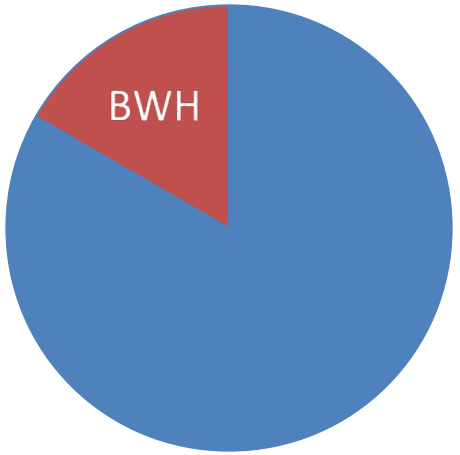
CSER Total recruitment – May, 2013

Reporting Incidental Findings

- All six CSER projects report incidental findings
- Half include IFs in their primary indication report, half have a separate report
- Half of sites allow opt out of medically actionable IFs
- 5/6 allow opt out of non-MA IFs







from H Rehm

What Categories of Incidental Findings are returned?

	Disease Risk	Carrier	PGx	Blood Group
Baylor	Yes	Yes*	Yes (3)	No
BWH	Yes	Yes	Yes (5/16)+	Yes
CHOP	Yes	Yes	No#	No
DFCI	Yes	Yes	Yes	No
UNC	Yes	Yes	Yes	No
UW	Yes	Yes	Yes (8)	No

*Only variants recommended for carrier screening by professional organizations such as ACMG or ACOG

+5 returned for all patients; 16 available upon request (with Sanger confirmation)

#PGx not returned due to focus on pediatric population

from H Rehm

What Types of Disease Risk Results are Returned?

Site	Predefined Gene List	Disease Risk Bins
Baylor	No	Medically actionable
BWH	No	Monogenic disease risk; Small-moderate cardiac risk
CHOP	Yes	Immediately medically actionable (MA), MA-childhood onset, MA-adult onset
DFCI	No	Genetic predisposition
UNC	Yes	Clinical utility (161 genes), Clinical validity (non-MA-Mendelian, untreatable neurodegenerative, GWAS)
UW	Yes (131)	High penetrance variants, Low penetrance variants

from H Rehm

Determining Actionability

- All groups use a multidisciplinary committee to either decide on a list of actionable genes or review variants on a case by case basis:
  - Case by case basis – Baylor, BWH, DFCI
  - *A priori* categorization of actionable genes (updated over time) – CHOP, UNC, UW

Variant Classifications Reported

- Generally, groups intend to return:
  - Pathogenic and VUS for primary indication
  - Pathogenic variants for IFs

- Biggest challenge:
  - What is sufficient evidence for pathogenicity?
    - Common evidence issues: “reported as pathogenic”; “segregates with disease in a family”

from H Rehm

Clinical Sequencing Exploratory Research

Genome Medicine 5

May 29, 2013

Bethesda, MD

genome.gov
National Human Genome Research Institute
National Institutes of Health