



Clinical Sequencing Exploratory Research (CSER) Program

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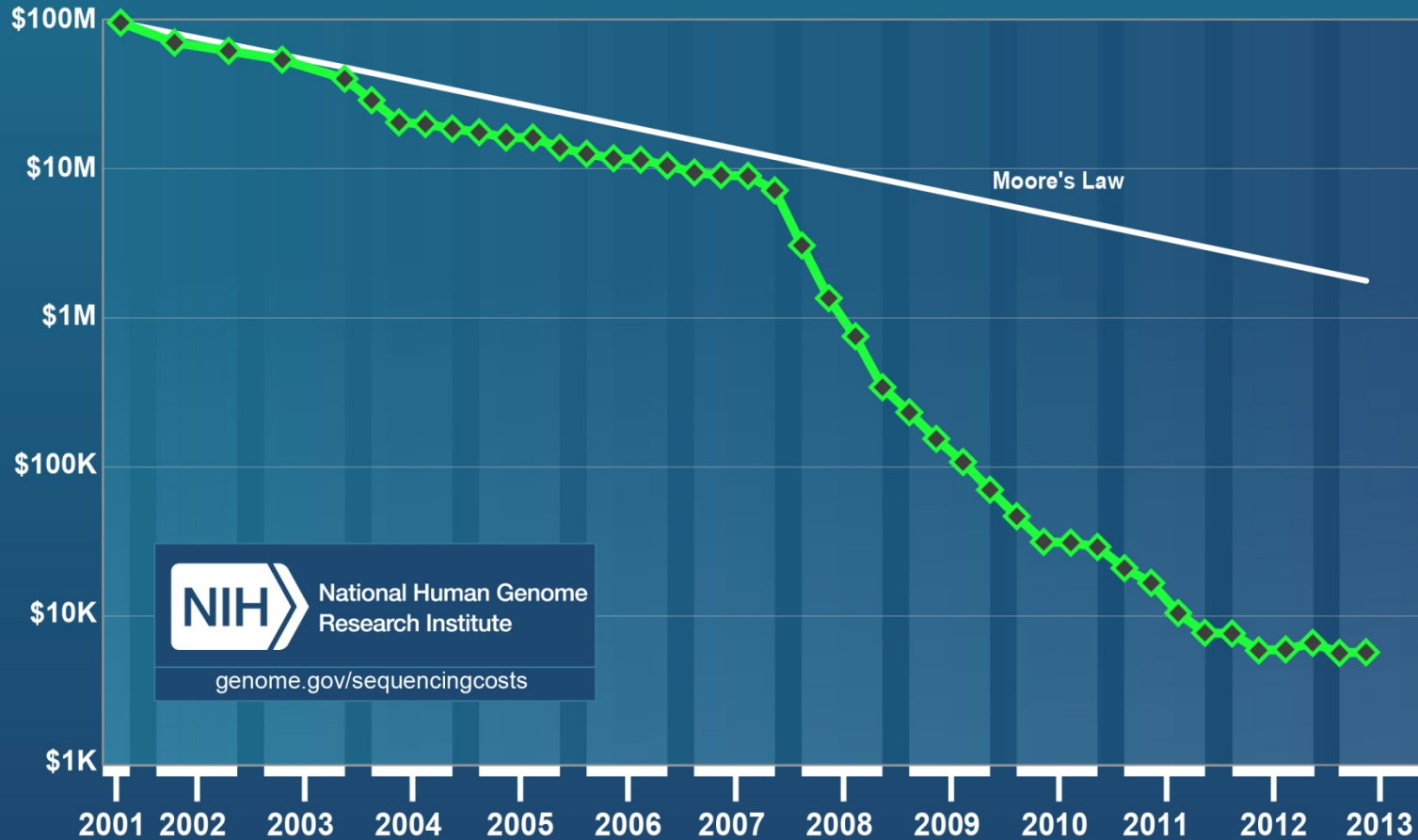
Global Leaders in Genomic Medicine

Washington, DC

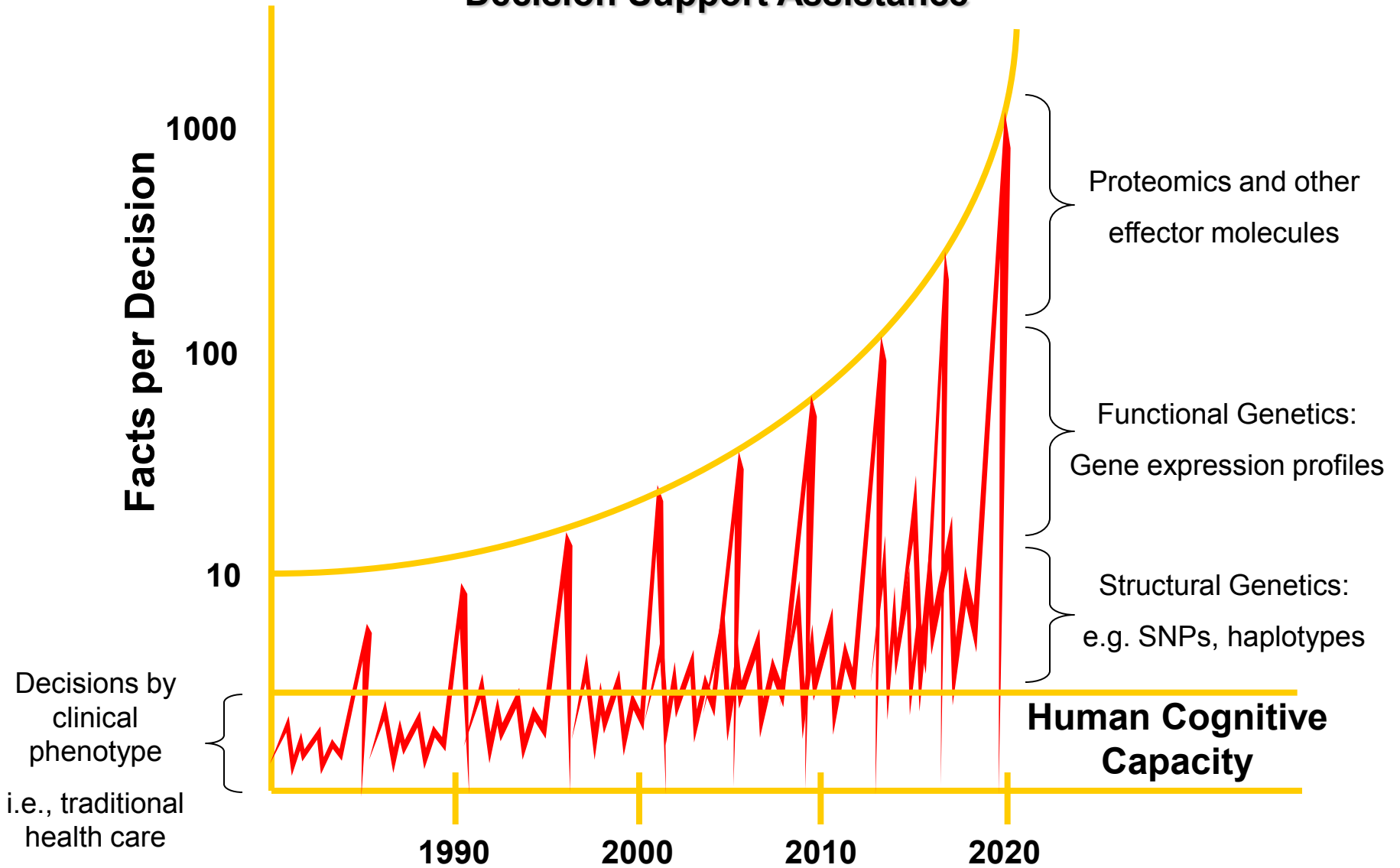
January 9, 2014



Cost per Genome



The Need for Patient- and Physician-Specific Decision Support Assistance



Decisions by
clinical
phenotype
i.e., traditional
health care

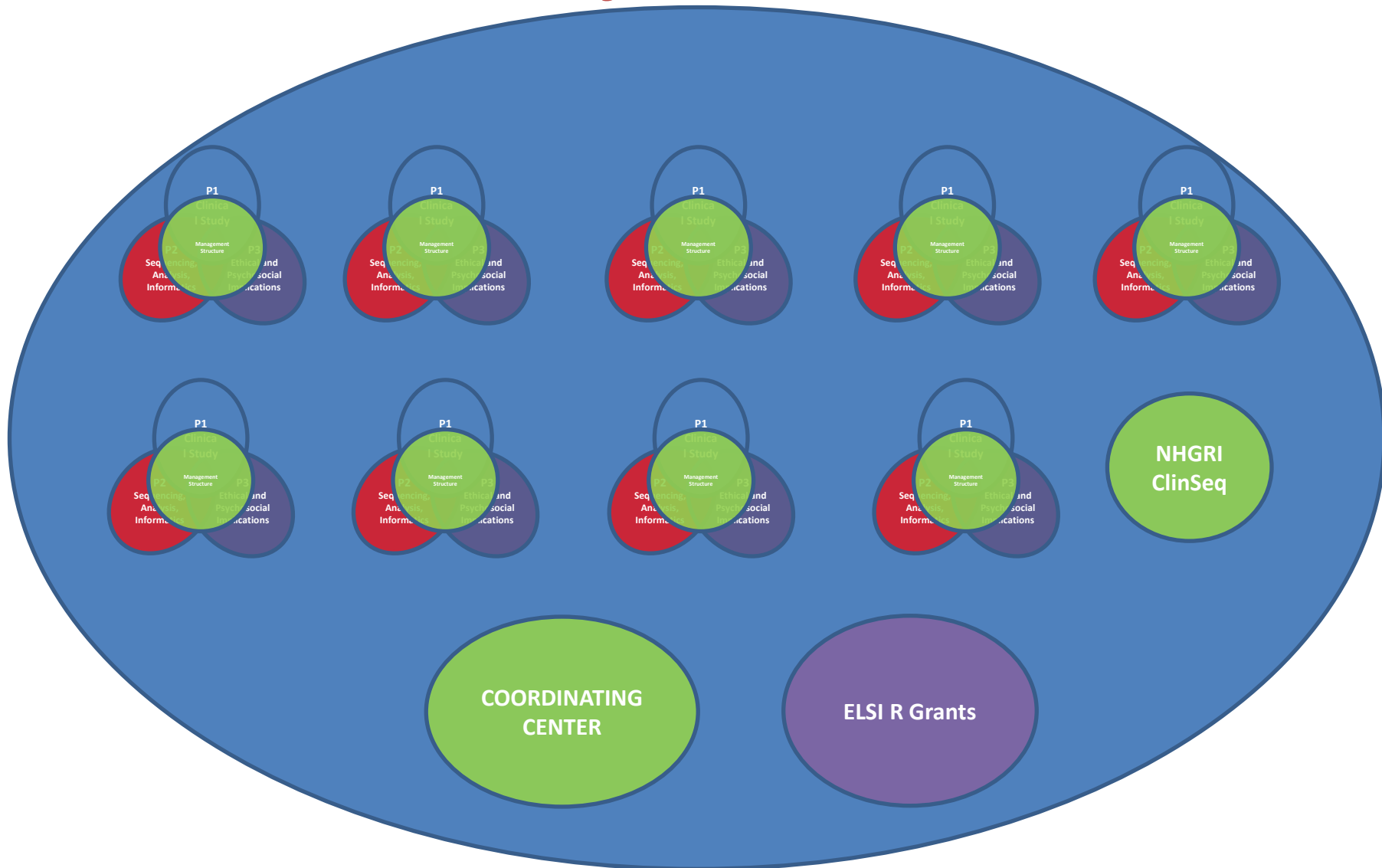
**Human Cognitive
Capacity**

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.

CSER Project Structure



CSER sites (U awards)

	Institution	Principal Investigator(s)	Disease Focus
2011	Baylor College of Medicine* <i>Houston, TX</i>	Sharon Plon, Will Parsons	Cancer (Pediatric)
	Brigham and Women's Hospital <i>Boston, MA</i>	Robert Green	Healthy; Cardiomyopathy
	Children's Hospital of Philadelphia <i>Philadelphia, PA</i>	Ian Krantz, Nancy Spinner	Pediatric Diseases
	Dana-Farber Cancer Institute / Broad Institute <i>Boston, MA</i>	Levi Garraway, Pasi Janne	Cancer
	University of North Carolina <i>Chapel Hill, NC</i>	James Evans, Jonathan Berg, Gail Henderson	Multiple
	University of Washington* <i>Seattle, WA</i>	Gail Jarvik	Cancer (Colorectal polyposis)
2013	HudsonAlpha Institute for Biotechnology <i>Huntsville, AL</i>	Richard Myers	Pediatric intellectual and developmental disability
	Kaiser Foundation Research Institute <i>Portland, OR</i>	Katrina Goddard, Benjamin Wilfond	Pre-conception genetic screening
	University of Michigan*	Arul Chinnayan	Cancer (sarcoma)

*co-funded by NCI



www.genome.gov/CSER
www.cser-consortium.org

CSER sites (R Grants)

PI	Title
Paul Appelbaum <i>Columbia University</i>	Challenges of informed consent in return of data from genomic research
Wendy Chung <i>Columbia University</i>	Impact of return of incidental genetic test results to research participants in the genomic era
Ellen Wright Clayton <i>Vanderbilt University</i>	Returning research results of pediatric genomic research to participants
Jeremy Garrett <i>Children's Mercy Hospital</i>	The presumptive case against returning individual results in biobanking research
Ingrid Holm <i>Boston Children's Hospital</i>	Returning research results in children: Parental preferences and expert oversight
Barbara Koenig <i>Mayo Clinic</i>	Disclosing genomic incidental findings in a cancer biobank: An ELSI experiment
Michelle Lewis <i>Johns Hopkins</i>	Return of research results from samples obtained for newborn screening
Richard Sharp <i>Cleveland Clinic</i>	Presenting diagnostic results from large-scale clinical mutation testing
Holly Tabor <i>Seattle Children's Hospital</i>	Innovative approaches to returning results in exome and genome sequencing studies

CSER Coordinating Center University of Washington

PI's	Areas of expertise	Key activities
Gail Jarvik, Wylie Burke, Deborah Nickerson, Peter Tarczy-Hornoch	Biostatistics, bioethics, cancer, clinical informatics, diagnostic testing, health care outcomes, medical genetics, neonatology, sequencing technology	<ul style="list-style-type: none">• Facilitate Working Group and cross-consortia collaborations• Coordinate, initiate, lead high priority CSER projects• Synthesize site-specific variant pathogenicity data, gene lists• Coordinate logistics for CSER Steering Committee, ELSI Committee, and working groups• Help raise consortium visibility

CSER Working Groups

- **Informed Consent & Governance**
Chairs: Paul Appelbaum and Joon-Ho Yu
- **Actionable Variants and Return of Results**
Chairs: Laura Amendola, Wendy Chung
- **Psychosocial Outcomes and Measures**
Chairs: Stacy Gray and Christine Rini
- **Sequencing Standards**
Chair: Donna Muzny and Nick Wagle
- **Electronic Reports/Medical Records**
Chair: Peter Tarczy-Hornoch and Brian Shirts
- **Phenotype Measures and Analysis**
Chairs: Ian Krantz and Peter White
- **Pediatrics**
Chairs: Kyle Brothers and Ben Wilfond
- **Genetic Counseling**
Chairs: Sarah Scollon and Denise Lauterbach

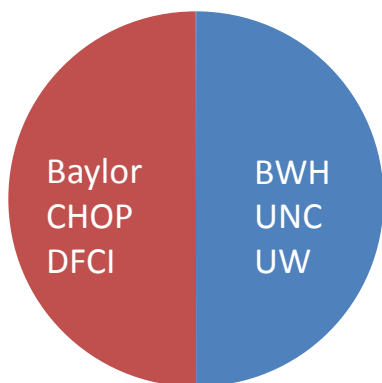


CSER recruitment December, 2013

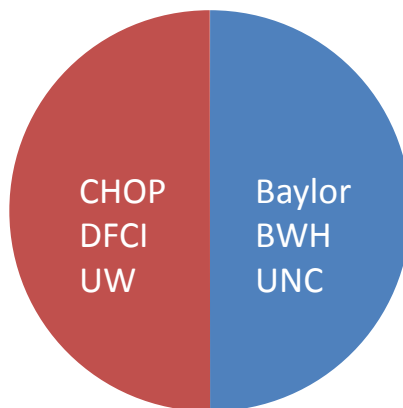
Patients/Participants			Physicians Enrolled
Contacted	Consented	Sequenced	
1,157	472	64 germline 114 tumor	116

Reporting Incidental Findings

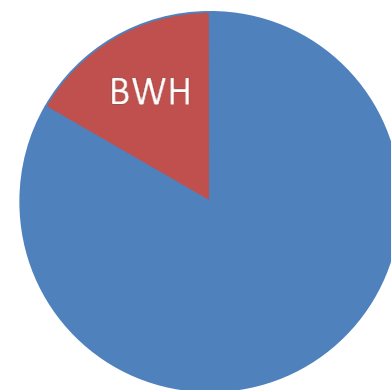
- All six CSER projects report incidental findings
- Half include IFs in their primary indication report, half have a separate report
- Half of sites allow opt out of medically actionable IFs
- 5/6 allow opt out of non-MA IFs



■ Separate Report
■ Combined Report



■ Can Opt-Out of MA IFs? Yes



■ Can Opt-Out of Non-MA IFs? Yes
■ Can Opt-Out of Non-MA IFs? No

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”

Recent work

Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence

A survey of informatics approaches to whole-

Recommendations for returning genomic incidental findings? We need to talk

ARTICLE

Lucia A
Sharon

The NEW ENGLAND JOURNAL of MEDICINE

Activating *ESR1* mutations in hormone-resistant metastatic breast cancer

Dan R Robinson^{1,2,12}, Yi-Mi Wu^{1,2,12}, Pankaj Vats^{1,2}, Fengyun Su^{1,2}, Robert J Lonigro^{1,3}, Xuhong Cao^{1,4}, Shanker Kalyana-Sundaram^{1,2}, Rui Wang^{1,2}, Yu Ning^{1,2}, Lynda Hodges¹, Amy Gursky^{1,2}, Javed Siddiqui^{1,2}, Scott A Tomlins^{1,2}, Sameek Roychowdhury⁵, Kenneth J Pienta⁶, Scott Y Kim⁷, J Scott Roberts⁸, James M Rae^{3,9}, Catherine H Van Poznak⁹, Daniel F Hayes⁹, Rashmi Chugh⁹, Lakshmi P Kunju^{1,2}, Moshe Talpaz⁹, Anne F Schott⁹ & Arul M Chinnaiyan^{1-4,10,11}

Breast cancer is the most prevalent cancer in women, and over two-thirds of cases express estrogen receptor- α (ER- α , encoded by *ESR1*). Through a prospective clinical sequencing program for advanced cancers, we enrolled 11 patients with ER-positive metastatic breast cancer. Whole-exome and transcriptome analysis showed that six cases harbored mutations of *ESR1* affecting its ligand-binding domain (LBD), all of whom had been treated with anti-estrogens and estrogen deprivation therapies. A survey of The Cancer Genome Atlas (TCGA)

tamoxifen and fulvestrant, are a mainstay of breast cancer treatment; however, approximately 30% of ER-positive breast cancers exhibit *de novo* resistance, whereas 40% acquire resistance to these therapies⁹. In addition to anti-estrogen therapies, patients with ER-positive breast cancer are also treated with aromatase inhibitors such as letrozole and exemestane¹⁰. Aromatase inhibitors block the peripheral conversion of androgens into estrogen and, in post-menopausal women, lead to over a 98% decrease in circulating levels of estrogen. As with anti-estrogens, treatment with aromatase inhibitors results in the



Clinical Sequencing Exploratory Research

Moving the Genome Into the Clinic

377 Researchers
20 Institutions
1 Consortium



North Carolina Clinical Genomic Evaluation by NextGen Home Sequencing

Jim Evans
Jonathan Berg
Gail Henderson

CanSeq

Levi Garraway



Robert Green



Gail Jarvik



The CHOP Pediatric Genetic Sequencing Project

Ian Krantz
Nancy Spinner

BASIC³

BCM Advancing Sequencing
Into Childhood Cancer Care

Sharon Plon
Will Parsons



Understanding the impact of genome
sequencing for reproductive decisions

Katrina Goddard
Benjamin Wilfond

HudsonAlpha

Rick Myers

MI-ONCOSEQ

Arul Chinnaiyan

R Grantees

Ingrid Holm
Paul Appelbaum
Wendy Chung
Jeremy Garrett
Michelle Lewis

Rich Sharp
Holly Tabor

Barbara Koenig, Gloria
Peterson, & Susan Wolf
Ellen Clayton & Bartha
Knoppers

NCI

Charlisse Caga-Anan
Sheri Schully

NHGRI

Jean McEwen
Carolyn Hutter
Kathie Sun
Teri Manolio
Brad Ozenberger (now at
WUSTL)



cser
Clinical Sequencing
Exploratory Research

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