Clinical Sequencing Exploratory Research (CSER) Program

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Division of Genomic Medicine, NHGRI

Global Leaders in Genomic Medicine
Washington, DC
January 9, 2014
The Need for Patient- and Physician-Specific Decision Support Assistance

Structural Genetics:
- e.g. SNPs, haplotypes

Functional Genetics:
- Gene expression profiles

Proteomics and other effector molecules

Human Cognitive Capacity

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

Facts per Decision

1000

100

10

1990 2000 2010 2020

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

Courtesy Dan Masys
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 sites (U awards)

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

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

<table>
<thead>
<tr>
<th>PI’s</th>
<th>Areas of expertise</th>
<th>Key activities</th>
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</table>
| Gail Jarvik, Wylie Burke, Deborah Nickerson, Peter Tarczy-Hornoch | Biostatistics, bioethics, cancer, clinical informatics, diagnostic testing, health care outcomes, medical genetics, neonatology, sequencing technology | • 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

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## CSER recruitment
### December, 2013

<table>
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<tr>
<th>Patients/Participants</th>
<th>Physicians Enrolled</th>
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<tbody>
<tr>
<td>Contacted 1,157</td>
<td></td>
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<tr>
<td>Consented 472</td>
<td></td>
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<tr>
<td>Sequenced 64 germline</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>114 tumor</td>
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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
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-genome sequencing for cancer care

Recommendations for returning genomic incidental findings: We need to talk

Activating ESR1 mutations in hormone-resistant metastatic breast cancer

Dan R Robinson1,2,12, Yi-Mi Wu1,2,12, Pankaj Vats1,2, Fengyun Su1,2, Robert J Lonigro1,3, Xuhong Cao1,4, Shanker Kalyana-Sundaram1,2, Rui Wang1,2, Yu Ning1,2, Lynda Hodges1, Amy Gursky1,2, Javed Siddiqui1,2, Scott A Tomlins1,2, Sameek Roychowdhury5, Kenneth J Pienta6, Scott Y Kim7, J Scott Roberts8, James M Rae3,9, Catherine H Van Poznak9, Daniel F Hayes9, Rashmi Chugh9, Lakshmi P Kunju1,2, Moshe Talpaz9, Anne F Schott9 & Arul M Chinnaiyan1,4,10,11

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

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