Genome resources at the University of Washington, Seattle

Gail Jarvik MD, PhD
Professor and Head, Div. Medical Genetics
Motulsky Chair in Medicine, Director, NWIGM,
on behalf of UW, Seattle
Outline

- Northwest Genome Center (Nickerson, Rieder)
  - Mendelian Genomic Center (PIs Nickerson, Rieder, Shendure, Bamshad)
    - SeattleSeqs; exome variant server
- eMERGE consortium (PIs Jarvik, Larson)
- CLIA sequencing
- Clinical sequencing study-NEXT Medicine (PI Jarvik; also Burke, Veenstra, Nickerson, Rieder, Fullerton, and others)
- Northwest Institute of Genetic Medicine
Next Generation Mendelian Genetics Center

- Successful Mendelian strategies
  - Group of unrelated patients with high locus homogeneity
  - Families, esp. recessive or linkage regions (Can have lod < 3)
  - Parent-child trios with a *de novo* mutations
- Validation/Replication is crucial for mutations identified in single families
- PIs Nickerson, Rieder, Bamshad, and Shendure
- Accepting unknowns!
Autism Trio-based Exome Sequencing

Simplified genetic model that focuses on single families & de novo mutations

Exomes solve a QTL:  
*LASS4* effects phospholipid transfer protein

Rosenthal et al. J Lipid Res. 2011  
52(10):1837-46. PMID:21757428
The goal of the NHLBI GO Exome Sequencing Project (ESP) is to discover novel genes and mechanisms contributing to heart, lung and blood disorders by pioneering the application of next-generation sequencing of the protein coding regions of the human genome across diverse, richly-phenotyped populations and to share these datasets and findings with the scientific community to extend and enrich the diagnosis, management and treatment of heart, lung and blood disorders.

The groups participating and collaborating in the NHLBI GO ESP include:

- Seattle GO - University of Washington, Seattle, WA
- Broad GO - Broad Institute of MIT and Harvard, Cambridge, MA
- WHISP GO - Ohio State University Medical Center, Columbus, OH
- Lung GO - University of Washington, Seattle, WA
- WashU GO - Washington University, St. Louis, MO
- Heart GO - University of Virginia Health System, Charlottesville, VA
- ChargeS GO - University of Texas Health Sciences Center at Houston

The group includes some of the largest well-phenotyped populations in the United States, representing more than 200,000 individuals altogether from:

- Women's Health Initiative (WHI)
- Framingham Heart Study (FHS)
- Jackson Heart Study (JHS)
- Multi-Ethnic Study of Atherosclerosis (MESA)
- Atherosclerosis Risk in Communities (ARIC)
- Coronary Artery Risk Development in Young Adults (CARDIA)
- Cardiovascular Health Study (CHS)
- Genomic Research on Asthma in the African Diaspora (GRAAD)
- Lung Health Study (LHS)
- Pulmonary Arterial Hypertension (PAH) population

Exome variant server interface
- 5400 exomes (to date) from NHLBI studies
Exome variant server LDLR query
http://evs.gs.washington.edu/EVS/

Gene Name: LDLR
Gene ID: 3949
Chromosome 19: 11200038 - 11244506 (+)
Population: EuropeanAmerican, AfricanAmerican

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<th>SNP Pos</th>
<th>rs ID</th>
<th>Alleles</th>
<th>EA Allele #</th>
<th>AA Allele #</th>
<th>All Allele #</th>
<th>Avg. Sample Read Depth</th>
<th>Genes</th>
<th>mRNA Accession #</th>
<th>GVS Function</th>
<th>Amino Acid</th>
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<th>Conservation</th>
<th>Grantham Score</th>
<th>Clinical Link</th>
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<td>-3.8</td>
<td>NA</td>
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eMERGE – www.gwas.net

- **eMERGE** – electronic MEdical Records and GEnomics Research Consortium
  - Cooperative Agreement of 7 Partner Institution
    - eMERGE1, Group Health/University of Washington, Marshfield, Mayo, Northwestern, and Vanderbilt
    - eMERGE2 added Geisinger and Mt. Sinai
    - NHGRI funded
  - to develop, disseminate, and apply approaches that combine DNA biorepositories with electronic medical record (EMR) systems for large-scale, high-throughput translational genetic and clinical genomic research
  - Plan deployment of the pharmacogenetics research network (PGRN) sequencing array
  - Strong bioethics component
CLIA sequencing at UW

- Peter Byers’ Collagen arrays, all genes
- Mary Claire King/Tom Walsh
  - 29 gene cancer array; 7 colon (Coloseq)
    - Primers available
  - Many other research interests
  - Current trial of 29 gene sequencing for new invasive breast cancer cases
- Laboratory Medicine
  - King/Walsh Coloseq chip, fee for service
    - King lab supports variant classification
- Coming soon: Nickerson/Rieder CLIA exomes, genomes!
Clinical sequencing in cancer: Clinical, ethical, and technological studies

NEXT Medicine (New Exome Technology)

- Project 1: Clinical Genomics study (Jarvik (PI), Veenstra, Patrick, Regier, Heagerty)
- Project 2: WXS (Nickerson, Reider)
  - Return of results process (Burke, Evans, Jarvik, Tarczy-Hornoch, et al)
- Project 3: Patient and clinician perspectives (Fullerton, Trinidad, Burke)
- Separate Return of Results RO1: Tabor
Study Rationale

- Familial CRCP is an ideal disorder to evaluate the utility of exomes for three reasons.
  - First, multiple genes are known to cause similar phenotypes.
  - Second, to arrive at a genetic diagnosis can be time consuming and expensive, requiring multiple clinical visits and tests as well as obtaining tumor samples for pathology studies.
  - Third, in as many as 50% of cases for which the clinician expects Lynch, the causative mutation is not identified.

- Thus WXS may offer more efficient and effective approach to identifying genetic causes of CRC.
Lynch Syndrome Screening (usual care)

High Clinical Suspicion of Lynch Syndrome/HNPCC?

Yes

Tier 1 Screening Tests

IHC: MLH1, MSH2, MSH6, PMS2

MSI testing

MSI-

Done

MSI+

Loss of MSH2, MSH6, or PMS2 by IHC

Loss of MLH1 by IHC or no MMR loss

Tier 2 Screening Tests

BRAF V600E

MLH1 Promoter Hypermethylation

BRAF-mutant or MLH1-methylated

DNA Sequencing of Appropriate Gene

BRAF-WT AND MLH1 not hypermethylated

No

Done

Pritchard and Grady. Gut (2011) Slide courtesy of Pritchard
Note that
- Usual Care (UC) may involve multiple visits for MSI/IHC and serial gene tests
- WXS arm includes UC
RCT Study Design

- Comparative
  - Usual care vs. whole exome sequencing (UC vs. WXS plus UC)
- Randomized
  - Control for confounding factors
  - Blinded until return visit (patient and clinician)
- Primary outcome
  - Proportion of patients with a causative genetic mutation identified
  - $N = 220$
  - 86% power to detect a 20% increase (50->70%)
- Unsolved cases move to a discovery aim, families collected
Patient reported psychosocial and economic outcomes

### Patient reported outcome psychosocial (PRO) measures

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<th>Measure</th>
<th># Items</th>
<th>Length</th>
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<td><strong>Symptoms</strong></td>
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<td>Anxiety symptoms</td>
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<td>2 minutes</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>9</td>
<td>2 minutes</td>
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<tr>
<td><strong>Perceptions</strong></td>
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<td></td>
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<tr>
<td>Self-rated health</td>
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<td>&lt;1 minute</td>
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<tr>
<td>Worry – genetic testing</td>
<td>16</td>
<td>3 minutes</td>
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<tr>
<td>Satisfaction – genetic testing</td>
<td>1</td>
<td>&lt;1 minute</td>
</tr>
<tr>
<td>Decisional conflict</td>
<td>3</td>
<td>1 minute</td>
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</table>

- Healthcare utilization followed by postcards of medical utilization
- Query regarding insurance changes, family members informed
- Also Discrete Choice Experiments (DCE) to value genetic services
Return of incidental exome findings: which?

- Clinical validity and utility (actionable)
- Committee of physicians (mainly medical geneticists) to “bin” results to be returned (Consortium work?)

<table>
<thead>
<tr>
<th>PANEL MEMBER</th>
<th>INSTITUTION, ROLE</th>
<th>EXPERTISE</th>
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</thead>
<tbody>
<tr>
<td>Wylie Burke MD PhD</td>
<td>UW, Co-Chair, Co-I</td>
<td>Medical genetics, internal medicine, bioethics</td>
</tr>
<tr>
<td>James P Evans MD PhD</td>
<td>UNC, Co-Chair</td>
<td>Medical genetics, genomics</td>
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<tr>
<td>Robin Bennett, MS, CGC</td>
<td>UW, Co-I</td>
<td>Genetic counselor, cancer genetics</td>
</tr>
<tr>
<td>Thomas Bird MD</td>
<td>VAMC Seattle</td>
<td>Neurogenetics, neurology</td>
</tr>
<tr>
<td>Peter Byers MD, PhD</td>
<td>UW, Co-I</td>
<td>Medical genetics, collagen/vascular, molecular lab</td>
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<tr>
<td>Frederick Chen MD</td>
<td>UW, consultant</td>
<td>Family medicine</td>
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<tr>
<td>William Grady, MD</td>
<td>UW, Co-I</td>
<td>Gastroenterology, Cancer</td>
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<tr>
<td>Fuki Hisama MD</td>
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<td>Medical Genetics, Neurology</td>
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<tr>
<td>Gail Jarvik MD PhD</td>
<td>UW, PI</td>
<td>Medical genetics, genomics</td>
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<tr>
<td>Katherine Leppig MD</td>
<td>Group Health, consultant</td>
<td>Medical genetics, cytogenetics, eMERGE RORC</td>
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<td>Jeff Murray, MD, PhD</td>
<td>Univ. Iowa</td>
<td>Medical genetics, pediatrics</td>
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<td>Wendy Raskind, MD</td>
<td>UW, consultant</td>
<td>Medical Genetics, General Int. Med, cancer</td>
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<td>Virginia Sybert, MD</td>
<td>UW, consultant</td>
<td>Medical &amp; Dermatological Genetics, Turner syndrome</td>
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<td>Benjamin Wilfond MD</td>
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<td>EXPERT ADVISORS</td>
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<td>Mark Rieder</td>
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<td>Debbie Nickerson</td>
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<td>S. Malia Fullerton</td>
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<tr>
<td>Genetic counselor,</td>
<td>TBN</td>
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</table>
Characterize patients’ and referring providers’ attitudes and preferences regarding the return of exome sequencing results (focus groups).

Explore patients’ views and experiences of receiving genetic test findings generated from exome sequencing:
- Elicit end-to-end first-person accounts from patients who receive both CRC and non-CRC risk information from exome sequencing, as well as the views of their referring providers.
- Describe and compare the experiences of patients who receive CRC risk information via exome sequencing to those who receive the usual-care workup for CRC risk.
- Describe and compare the views and experiences of patients who receive different types of exome sequence information (unrelated to CRC risk).

Legal analysis of whether a requirement for CLIA compliance as a precondition to returning results from genomic research studies violates the First Amendment (Barbara Evans, JD, U Houston).
Partial Acknowledgements

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Mark Rieder
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Mike Bamshad
Evan Eichler

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Dave Veenstra
Wylie Burke
Malia Fullerton
Donald Patrick
Chris Nefcy
Peter Byers
Dean Regier
Fuki Hisama
Peter Tarczy-Hornoch
Brian Browning
Patrick Heagerty
Robin Bennett
Barbara Evans, JD
Clinical review committee
Enrollment

- In (first) clinic visit
- Subjects with CRCP where a single gene is not highly implicated
  - Exclude
    - Very likely APC (>100 polyps?)
    - Known mutation in family
    - Syndromic features suggest the diagnosis
Who and when enrolls

- GCs can enroll
- Fulltime (junior) GC to support study
- Martha can enroll
- Enroll and randomize at first visit
Clinically, what then

- Randomized to UC or WXS plus UC
- For both do your usual protocol (let's discuss)
- For WXS they have a blood test for exome
- Return to clinic for UC billed visits
- Each will have 1 extra, non-billed visit
  - Incidental Exome findings for WXS
  - Review of family risks for UC
Patient Outcomes

- Prior studies of CRC genetic testing report distress and anxiety scores within normal limits or moderately increased following disclosure of results.
- Collins et al. reported an increase in cancer-specific distress in carriers at 2 weeks post-disclosure, followed by a return to baseline levels at 12 months that was stable 3 years later.
- Several studies have identified demographic and psychological factors (e.g., baseline mood disturbance, state anxiety, cancer worry, resilience, cognitive style, coping style) that are correlated with increased distress.
- Given the potential extensive scope of incidental findings from exome sequencing, these effects warrant further study.
Follow psychosocial and economic outcomes

- Healthcare-related resource utilization (HRU) will be collected using a patient survey implemented with a postcard [online?] return every month.
- Patients will be asked about:
  - use of medical services such as physician visits, hospitalization, prescription and non-prescription drug use, screening, ancillary care, and mental health services.
  - how many family members they have informed of their test results, and what actions their family members have taken to their knowledge – e.g., received genetic testing or CRC screening.
  - actual or intended changes to their health and life insurance policies.
Discrete Choice Experiments (DCEs)

- DCEs assume
  - that health care ‘goods’ can be described by two or more attributes (e.g., probability of finding a genetic risk of CRCP; time waiting for results; cost of testing),
  - that each attribute is defined on a number of levels (e.g., 40% chance, 80% chance; 2 weeks, 8 weeks; $750, $2000)
How to find a needle in a haystack?

~1 *de novo* event expected per trio
16,000-20,000 exome variants
20 Pilot Trios

**FOXP1**
- A339SfsX4

**GRIN2B**
- 3'-splice

**SCN1A**
- P1894L

**LAMC3**
- D339G

O’Roak et al. Nat Gen. May
Exome sequencing is transforming Mendelian Genetic Analysis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mode</th>
<th>N</th>
<th>Strategy</th>
<th>Gene(s)</th>
<th>PMID</th>
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<td>Hadju-Chenev</td>
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<td>Fowler</td>
<td>AR</td>
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**Comparison of related cases**

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<td>novel skeletal dysplasia</td>
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**Homogygosity mapping**

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<td>Seckel</td>
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<td>NPHP-related ciliopathy&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Ochoa</td>
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**Identification of de novo mutations**

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<td>sporadic MR</td>
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<td>30</td>
<td>10 parent-child trios</td>
<td>multiple</td>
<td>21076407</td>
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<td>autism</td>
<td>complex</td>
<td>60</td>
<td>20 parent-child trios</td>
<td>multiple</td>
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Why Exomes?

Advantages:

- More interpretable
- Easier to follow up
- Larger effect size
- Cheaper and sample size counts

Disadvantages:

Miss non-coding variants and some coding
We do genomes when we need to!
Some of the Challenges in Exome Analysis

- Undercalling of coding variants (SNVs, indels, and CNVs)
- Causal non-coding
- Soft phenotyping and/or modifiers
- Genetic heterogeneity at all levels
Genetics of Autism

- Strong genetic component ~70-90%
- Linkage and GWAS have uncovered few consistent genes or regions
- Likely widespread heterogeneity
- How do we get at the 70% of unknown causes?

*Modified from Schaaf and Zoghbi 2011
Apply a de novo variant approach

Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome

Ng et al. Nat Genet, Aug 2010

A de novo paradigm for mental retardation

Vissers et al. Nat Genet, Nov 2010

Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations

Trio Based Exome Sequencing

- **Raw Reads**: 18,816
- **Mapped Reads**: 50-100
- **Possible SNVs, Indels, & CNVs**: 2
- **Possible De Novo Events**: 1.5
- **Annotated and filtered variants**: 1.3

SNV and indel (Nimblegen v2)

Raw *de novo* - Screen against other exomes

*Candidate de novo* - Manual review

Sanger confirmation

Confirmed *de novo* per trio
Drug Metabolism: Cytochrome P450s

• Oxidize many biological substances using heme cofactor

• Small handful of CYPs responsible for 75% of drug responsiveness in humans

• Genetic variation in drug response responsible for up to 30% of all ADRs

Evans & Relling Science (1999)
Coding Variation in CYP2C19
(Plavix, Warfarin, Valium)

113 Val → Ile
7 AA
Heme binding residue

155 Glu → Stop
1 AA
Truncates protein

147 Glu → Gly
147 Glu → Gln
1 EA (each)
Substrate binding site component

160 Lys → Glu
1 AA
Highly conserved position

344 Asn → Ile
1 EA
Substrate binding residue

432 Lys → Ile
9 AA
Heme binding residue

147 Glu → Gly
147 Glu → Gln
1 EA (each)
Substrate binding site component

dbSNP (* = functional)

ESP2500
ESP5400
SeattleGO
Debbie Nickerson
Mark Rieder
Jay Shendure
Phil Green
Josh Akey
Mike Bamshad
Carlos Bustamante
Evan Eichler
Suzanne Leal
Bryan Paeper
Peggy Robertson
Josh Smith
Emily Turner

BroadGO
David Altshuler
Stacey Gabriel
Goncalo Abecasis
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Charles Kooperberg
Ethan Lange
Leslie Lange
Yun Li
Danyu Lin
Keri Monda
Alex Reiner
Kira Taylor
CFTR

CF allele freq in US

Mutation Allele Frequency

Mutation Allele Frequency Without Δ508

- 405+3A®C
- DF311
- 2307insA
- 2183AA®G
- I506T
- 2055del9®A
- 406-1G®A
- 711+1G®T
- 2184delA
- 3659delC
- 406-1G®A
- 711+1G®T
- 2184delA
- 3659delC
- 2789+5G®A
- 1898+1G®T
- 3849+10KbC®T
- 621+1G®T
- N1303K
- G551D
- G542X
- DF508
**Gene Name:** LDLR

**Gene ID:** 3949

**Chromosome 19:** 11200038 - 11244506 (+)

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### Select Data Set(s)

Check at least one data set below.

<table>
<thead>
<tr>
<th>Select</th>
<th>Number Variations</th>
<th>Population</th>
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<td>EuropeanAmerican</td>
</tr>
<tr>
<td>✔️</td>
<td>121</td>
<td>AfricanAmerican</td>
</tr>
</tbody>
</table>

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### Display Results

- [display snp summary](#)

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[reset](#)
In an African American patient with FH (143890), Leitersdorf and Hobbs (1990) found a change of aspartic acid-283 (GAC) to asparagine (AAC).

This and the asp206-to-glu mutation (see 606945.0006) are frequent among Afrikaners with FH (143890). A GTG-to-ATG mutation is responsible (Leitersdorf et al., 1989). In a study of 138 chromosomes of Afrikaner FH patients, Kotze et al. (1991) found that 31 (23.3%) had this mutation. Schuster et al. (1993) found the same mutation in a German family and showed that it existed on the same 7-RFLP haplotype as did the mutation described in South Africa and in the Netherlands, suggesting a common European origin. Similarly, Defesche et al. (1993) found the val408-to-met mutation in 19 (1.5%) of 1,268 FH patients of Dutch descent. In 9 of the patients carrying this mutation on one allele, the LDLR DNA haplotype was that observed in a South African FH patient homozygous for the same mutation. The remaining 10 Dutch FH patients all shared a common haplotype, partly identical to the Afrikaner haplotype, which could have arisen from a single recombinational event. With the exception of the family reported by Schuster et al. (1993), this mutation has been described only in persons of Dutch ancestry.

A GCT-to-ACT change is responsible for this variant (Zuliani and Hobbs, 1990).
Lots of people

Gail Jarvik
David Veenstra
Wylie Burke
S. Malia Fullerton
Debbie Nickerson
Mark Rieder
Fuki Hisama
Peter Tarczy-Hornoch
William Grady
Wendy Raskind
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GC to write blurbs
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Chris Nefcy
Susan Trinidad
Josh Smith
Bryan Paeper
Jeff Furlong
Peggy Robertson
Katie Igartua
CLIA Compliance Officier
MITS Clinical Computing Dev
Grad student RA for Outcomes
Exome

- 180,000 exons in human genome
- 1% of the human genome
- 30 megabases (Mb)
  - 30M results?
- Estimated to constitute about 85% of the disease-causing mutations
RFA -> UO1 Proposal

- **Project 1**
  - Clinical Genomics study (Jarvik (PI), Veenstra, Patrick, Regier, Heagerty)

- **Project 2**
  - WXS (Nickerson, Reider)
  - Return of results process (Burke, Jarvik, et al)

- **Project 3**
  - Patient and clinician perspectives (Fullerton, Trinidad)