Enabling Precision Genomics

Department of Medicine Grand Rounds
University of Cincinnati College of Medicine

December 2, 2015
Precision Medicine

DRUGS USED TO BE DESIGNED WITH THE AVERAGE PATIENT IN MIND
NOW, THEY CAN BE TAILORED TO SPECIFIC PATIENTS' GENETICS, MICROBES, AND CHEMICAL COMPOSITION

SOURCE: HHS
Imagine

Being able to diagnose your baby’s treatable metabolic disease before they are born

Selecting the best medication and dose to treat your child’s newly diagnosed cancer or their depression without a diagnostic and treatment odyssey

Being able to prevent your child from developing obesity and diabetes

Curing your child’s sickle cell anemia or cystic fibrosis before it destroys their life
Genomic disease at CCHMC

35-50% of inpatient admissions

> 50% of charges

40% of CCHMC grants include genomics

44 Divisions are included
Down Syndrome, Type 1 Diabetes, Schizophrenia, Graves Disease, Epilepsy, ADHD, Polycystic Ovary Syndrome, Celiac Disease, Obesity, Bipolar Disorder, Alzheimer Disease, Psoriasis, Autism, Breast Cancer, Rheumatoid Arthritis, Lupus, Depression, Heart Disease, Prostate Cancer, Ovarian Cancer, Stroke, Osteoarthritis, Hypertension, Asthma, Type 2 Diabetes
“In 2010, the total “hidden” cost of ADHD to the economy was estimated to be between $143 billion and $266 billion, or roughly $1,260 to $2,360 per household.”
--NEA today

“The estimated annual health care costs of obesity-related illness are a staggering $190.2 billion or nearly 21% of annual medical spending in the United States.”
--ScienceDaily.com

“New Research Finds Annual Cost of Autism Has More Than Tripled to $126 Billion in the U.S.”
--Autism Speaks
What does precision genomics require?

• Patients and data
  – Volume
  – Veracity
  – Variety
• Strong and diverse expertise base
• Translation and implementation science capacity
• Access to distributed research networks
What does precision genomics require?

- Patients and data
  - Volume
  - Veracity
  - Variety
- Strong and diverse expertise base
- Translation and implementation science capacity
- Access to distributed research networks
- **Self-awareness** of capability, capacity, opportunity
- Organizational and operational **cohesion**
- High level of **transparency**
- **Trust**-based culture
The leaders will be able to:

- Rapidly deliver organized data
- Rapidly translate to actionable knowledge
- Rapidly disseminate individualized care
- Have the organizational structures needed for success
The best model for precision genomics is?

• Traditional model: Focused
  – Investigator-driven
  – Scale, complexity, and expertise challenges

• Current model: Centralized
  – Agency or institute-driven
  – Incentivization and innovation challenges

• Emerging model: Peer-driven
  – Team science
  – Organizational and social challenges
Vibrant social fabrics provide cohesive strength

...and align with the future of genomic medicine
Key Cincinnati Children’s Systems:

- Healthcare learning systems
- Clinical and Translational Science Award
- Molecular disease networks
- Center for Pediatric Genomics
- Genomic Research and Innovation Network
Healthcare Learning Systems

- Enhanced disease registries
- Patient-focused
- Participatory
- Common data models and practice
- QI, Safety, Research, Operations
- Network-based clinical research
  - SafetyNet
  - ImproveCareNow (Inflammatory Bowel Disease)
  - PEDSNet (many pediatric disorders)
Clinical and Translational Science Award

- NIH NCATS network
- Infrastructure for enabling best clinical & translational science
- 62 participating sites
- Cincinnati: model for cooperative research
  - Engage
  - Empower
  - Educate
Molecular Disease Networks

- eMERGE III
- Bench to Bassinet Program
- Newborn Screening Translational Research Network
eMERGE III

- Electronic Medical Records and Genomics
- Computable Phenotypes
- Genomic screening of targeted disorders
  - Appendicitis
  - Methylphenidate and ADHD
  - Malignant hyperthermia
  - Pain-related disorders
- 20,000 samples for panel sequencing
- Return of results
23000 subjects
9000 genomes
140 TB of data
$146M
Discover Harvest

Explore your data, not your database.

Designed by and for biomedical researchers, The Harvest Stack is an open source BSD-licensed toolkit for building web applications for integrating, discovering, and reporting data.

Open Source & Available on GitHub
We believe in open source software and open-source our work. Harvest is licensed under BSD 2-clause License.

Designed for Biomedical Data First
Created by the Center for Biomedical Informatics at The Children’s Hospital of Philadelphia Research Institute, Harvest addresses the unique needs of biomedical researchers.

Web-Based Technologies
Harvest comes with an HTML5 web client backed by a set of discoverable REST APIs.

Nationally Funded
National Human Genome Research Institute (NHGRI), National Institute on Deafness and Other Communication Disorders (NIDCD), National Heart, Lung and Blood Institute (NHLBI), and others have funded Harvest applications.

Pennington et al, JAMIA, 2014
Heterotaxy

Heterotaxy per B2B Comm definition, based on Fyler codes and extracardiac findings

Unique values: 2

- False: 7067 (91%)
- True: 677 (8%)

Update Filter
Query:
Subjects with heterotaxy
No evidence of structural heart disease in either parent
Pathogenic variants in genes KCNA1, CFC1, FOXH1, GDF1
Bench to Bassinet Outcomes

- *de novo* mutations in $H3K4$ methylation
- Increased rare *de novo* CNV burden
  - PCGC et al, Circ Res, 2014
- Re-use of accrued data
Newborn Screening

Diagnosis and Referral

Pediatric Specialty Care, Medical Home

Transition to Adulthood

Adult Specialty Care, Medical Home
• NICHD
• Longitudinal Pediatric Data Resource
• National consensus committees
  – 52 disorders: metabolic, LSDs, SMA
  – 1800 common data elements
  – 9000 disorder-specific elements
• Collection, management, query, exploration
  – 1800 subjects
  – Metabolic → genomic (NSIGHT)
Center for Pediatric Genomics
A community of genomics practice

- Incubate the best science
- Build a genomics community of diverse stakeholders
- Increase institutional genomic literacy
- Coalesce data, technology, and capability
Opportunity

How can we expand upon our success?

- Shared resources
- Well-defined processes
- Knowledge transfer
- Team science
- Eye on the patient
- ...across the AHC
Incubate the Best Science

• Supported projects: complete an “arc”
  – Patient and genomic discovery
  – Validation of pathogenic candidates
  – Return of results and clinical intervention

• Methods and technology

• Centralized facilitation
<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
<th>Project Description</th>
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<tbody>
<tr>
<td>Ken Kaufman</td>
<td>Rheumatology</td>
<td>AGER hereditary pulmonary alveolar proteinosis</td>
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<tr>
<td>Jim Wells</td>
<td>Dev Biology</td>
<td>Corrected beta cells in diabetes</td>
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<tr>
<td>Steve Potter</td>
<td>Dev Biology</td>
<td>Hepatoblastoma and congenital kidney disease</td>
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<td>Sonata Jodele</td>
<td>Bone Marrow</td>
<td>Predisposition for thrombotic microangiopathy</td>
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<td>Rolf Stottmann</td>
<td>Human Genetics</td>
<td>Congenital craniofacial malformations</td>
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<tr>
<td>Hansel Greiner</td>
<td>Neurology</td>
<td>Focal cortical dysplasia</td>
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<td>Senthil Sadhasivam</td>
<td>Anesthesia</td>
<td>EMR machine learning, postoperative pain and opioids tonsillectomy</td>
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<tr>
<td>Taosheng Huang</td>
<td>Human Genetics</td>
<td>SLC25A46 in autosomal recessive optic atrophy and axonal neuropathy</td>
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<td>Kasiani Myers</td>
<td>Bone Marrow</td>
<td>Inherited bone marrow failure</td>
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<td>Chunyue Yin</td>
<td>Gastroenterology</td>
<td>Progressive familial intrahepatic cholestasis patients</td>
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<tr>
<td>Derek Neilson</td>
<td>Human Genetics</td>
<td>A painful syndrome: Ehlers Danlos Hypermobility Type</td>
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Genetic Analysis of Human Craniofacial Malformations

6 months
Cleft lip and cleft palate

Mouse model

Repaired
(16 months)
Genetic Analysis of Human Craniofacial Malformations

Family identified → CCHMC services → Next-Generation Sequencing

- Identify basic principles
- Design innovative treatments
- New treatments
- Counseling of risks
- Analyze findings
- Generate hypotheses
- Experimental models
Therapeutic repair of severe diabetes by altering cellular genetics

Aim 1
Dolan Dauber

Whole exome sequencing
Identification of mutations

Generation of induced pluripotent stem cells

Correct genetic mutation using CRISPR

Aims 1&2
Wells

Corrected iPSCs

Differentiation into pancreatic beta cells

Study beta cell function in vitro

Study beta cell function in vivo

Long term goal:
autologous transplantant
of corrected beta cells
into patients with diabetes

Identify and recruit patients with diabetes

skin blood etc.
Building a genomics community

- Saturating communication
- Alignment with existing programs
- Phenotype Phorum
  - Clinician success stories
  - Responder/non-responder opportunities
- Project workgroup
- Analyst awareness
- Expertise profiling/matching
Increasing Genomic Literacy

Foundational genomics
• Clinicians
• Clinical staff
• Basic researchers
• Translational researchers
• Patients/families

Advanced genomics
• Integration with formal educational programs
Coalesce data, technology, and expertise

• Sequence metadata model
• Unified sequence intake/processing
• Annotated variant knowledgebase
• Integration with RIT structure & analytical capabilities
• Research and clinical genomics
• Layering on additional -omics
The Genomics Research & Innovation Network
Genomic Research and Innovation Network

Key Outcomes:

• Provide a common, shared community of practice for collaborative genomic studies
• Create a broad knowledgebase of annotated genomic and clinical data for variant interpretation
• Establish a “big data” environment to benefit discovery, translational science, and trainee development
• Facilitate cohort expansion – especially valuable in the study of rare disease
• Enhance team science by matching disparate disease and analysis experts around genomic challenges
Phenotype data from
- Electronic Health Records
- Clinical trials
- Data registries

Other data (other -omics, imaging, physiologic measurements (EKG, EEG)

Data Trust

Genomic Data

BCH

CHOP

CCHMC
GRIN Data Trust Structure

- Commercial/Research Collaborations
- Patient/Disease Foundations
- Grants
- Philanthropy

Institutional/PI control over sharing of data, samples

- BCH
- CCHMC
- CHOP

PI PI PI PI PI PI
Phase I: GRIN Pilot Projects

• Three projects, each involving investigators from the three founding GRIN institutions
  – Obesity
  – Epilepsy
  – Growth disorders

• Scientific results are NOT the only success metric

• Pilot goals:
  – Demonstrate the value of GRIN services
  – Learn how collaboration on this scale is possible
  – Inform development of the GRIN infrastructure
Opportunities

• Distributed analysis of complex diseases
• Patient-level stratification
• Literate communities
• Precision care delivery and support

Challenges

• Literacy
• Communication
• Behavioral economics
# Network-based research

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<tr>
<th>eMERGE</th>
<th>Bench to Bassinet</th>
<th>NBSTRN</th>
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<tr>
<td>Armand Antommaria</td>
<td>Rachel Akers</td>
<td>Bruce Bowdish</td>
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<td>Beth Cobb</td>
<td>Jim Cnota</td>
<td>Amy Brower</td>
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<td>Eric Hall</td>
<td>Stacy France</td>
<td>Irina Butler</td>
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<tr>
<td>John Harley (PI)</td>
<td>Nathan Hawk</td>
<td>Chris Day</td>
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<td>Ken Kaufman</td>
<td>Stephen Hope</td>
<td>Nick Felicelli</td>
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<td>Leah Kottyan</td>
<td>Bridget Kellner</td>
<td>Rachel Fleming</td>
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<tr>
<td>Sara Lazaro</td>
<td>Eileen King (co-PI)</td>
<td>Steve Grimaldi</td>
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<td>Nancy Leslie</td>
<td>Mojtaba Kohram</td>
<td>Michael Kuhlmann</td>
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<td>Todd Lingren</td>
<td>Michal Kouril</td>
<td>Guillaume Labilloy</td>
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<td>Keith Marsolo</td>
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<td>Chunyan Liu</td>
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<td>Melanie Myers</td>
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<td>Lauren Lykowski</td>
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<td>Bahram Namjou-Khales</td>
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<td>Lisa Martin</td>
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<td>Yizhao Ni</td>
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<td>Diana McClendon</td>
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<td>Bill Nichols</td>
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<td>Nick Ollberding</td>
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<td>Cindy Prows</td>
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<td>Andy Rupert</td>
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<td>Senthilkumar Sadhasivam</td>
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<td>Prakash Valayutham</td>
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<td>Scott Wexelblatt</td>
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<td>Michael Wagner (co-PI)</td>
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<td>Pete White</td>
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<td>Mike Watson</td>
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<td>Pete White (co-PI)</td>
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## Our Community

### Leadership
- Peggy Hostetter (co-sponsor)
- Jennifer Dauer (co-sponsor)
- Tracy Glauser
- Arnie Strauss
- John Harley (co-chair)
- Pete White (co-chair)
- CCHMC Board of Trustees

### Steering Committee
- Armand Antommaria
- Daniel Choo
- Rafi Kopan
- Nancy Leslie
- Lou Muglia
- Bill Nichols
- John Perentesis
- Cindy Prows
- Niki Robinson
- Sarah Savage
- Harinder Singh
- Tom Stroeh
- Kristen Sund
- Jessica Woo

### Scientific Project Leads
- Hansel Greiner
- Taosheng Huang
- Sonata Jodele
- Ken Kaufman
- Kasiani Myers
- Derek Neilson
- Steve Potter
- Senthil Sadhasivam
- Rolf Stottrmann
- Jim Wells
- Chunyue Yin

### Community and Learning
- Jane Garvey
- Missy Kasota
- Jim Saporito
- Beth Sims
- Ryan Varney
- Jill Williams

### Informatics
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- Bruce Aronow
- Eric Bardes
- Artem Barski
- Jing Chen
- Phil Dexheimer
- Nick Felicelli
- David Fletcher
- Anil Jegga
- Mojtaba Kohram
- Guillaume Labilloy
- Sara Lazaro
- Keith Marsolo
- Andrew Rupert
- Mayur Sarangdhar
- Scott Tabar
- David Van Horn
- Michael Wagner
The GRIN Team

Steering Team
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Ken Mandl
Joe Majzoub
Nancy Spinner
Joe St. Geme
Arnie Strauss
Pete White
Bryan Wolf

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Sarah Savage
Kristen Sund

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David Bernick
Jon Bickel
Michal Kouril
Jeremy Leipzig
Keith Marsolo
Adam Resnick
Deanne Taylor
Pete White
Tim Yu

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Joan Gates
Matthew Hodgson
Chris Kirby
Susan Kornetsky
Dianne McCarthy
Peter Naderer
Amy Schwarzhoff
Gelvina Stevenson
Wendy Wolf

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Tracy Glauser
Anna Poduri
Vidhu Thacker
Struan Grant
John Harley
Andrew Dauber
Adda Grinberg
Joel Hirschhorn

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Gus Cervini
Matt Cook
Linda Miller
Chris Kirby
David Margulies
Niki Robinson
Bryan Wolf
Alan Yen