Moving Genomics to General Practice
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Genomic Medicine Institute
MyCode Return of Results Program

- 200,000+ consented
- 140,000 sequenced
- 1000+ results returned
- Return results for all ACMG reportable conditions

**MyCode® results reported**
877 patient-participants have received results from the Genomic Screening and Counseling Program

For the latest results, see geisinger.org/MyCode-results.

**CDC tier 1 conditions (click link)**

<table>
<thead>
<tr>
<th>Risk condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>272</td>
<td>BRCA1</td>
<td>93</td>
</tr>
<tr>
<td>(early breast, ovarian, prostate and</td>
<td></td>
<td>BRCA2</td>
<td>179</td>
</tr>
<tr>
<td>other cancers)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>111</td>
<td>APOB</td>
<td>32</td>
</tr>
<tr>
<td>(early heart attacks and strokes)</td>
<td></td>
<td>LDLR</td>
<td>79</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>96</td>
<td>PMS2</td>
<td>30</td>
</tr>
<tr>
<td>(early colon, uterine and other</td>
<td></td>
<td>MSH6</td>
<td>49</td>
</tr>
<tr>
<td>cancers)</td>
<td></td>
<td>MSH2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>881</strong></td>
<td></td>
<td><strong>881</strong></td>
</tr>
</tbody>
</table>
Precision Health Pilot

- Preventative measure
- 1000 patients sequenced as a routine part of clinical care
- Offered through patient’s primary care provider
- Return results for all ACMG reportable conditions
Genetics by the Numbers

- 46 Chromosomes
- ~20,000-23,000 genes
- ~3 billion base pairs in the human genome
- BRCA2 is 83,736 base pairs
- Every time you have a child they will incur 100 to 200 new mutations
- Mutation rate increases with the age of the father
Genetic mutations do not usually give you super powers
What your genes can tell physicians

• What diseases you are likely to develop
• How you will react to medication
• How you will respond to infectious diseases
• How you will behave
• How you will sleep
• What you eat
What is Medical Genetics/Genomic Medicine

• Started in the late 1940s
• Did not require an MD – PhDs were often practitioners
• Dysmorphologists – Syndrome identification
• Familial risk identifiers

We did not even know how many chromosomes we had until 1956
First disease gene mapped in 1983
Pop Quiz! -

In what decade was the following statement printed?

“Of all the applications of medical genetics, the one potentially most valuable is in the field of preventative medicine.”
In what decade was the following statement printed?

“Of all the applications of medical genetics, the one potentially most valuable is in the field of preventative medicine.”

Answer: 1946
The Role of a Clinical Geneticist

- Diagnosis
- Management
- Prevention
- Risk Assessment
- Counseling
Challenges in Clinical Genetics

- More than 6000 known genetic disorders
- Nationwide shortage of clinical geneticists
- Getting more referrals from specialists
- Shortage of genetic counselors
Challenges in Clinical Genetics

- Healthy people getting direct to consumer tests
  - MTHFR challenge
- Poor reimbursement for testing and services
- Uncertainty in classification of variants and diagnosis
- Poor access to data that is crucial in our field
- Up to one year wait times to see a geneticist
Physicians outside of clinical genetics are not prepared to understand, deliver or manage genetic test results.
Systems that allow physicians access to quick and accurate knowledge about genetic conditions are the only way to solve this information overload.

No one can acquire and maintain the knowledge to diagnose and manage over 10,000 diseases.
Genomic medicine will move from a specialty which did not even require an MD degree to become an integral part of practice that is required of everyone with an MD degree.
Found to have a pathogenic variant in BRCA1
Elected to have a bilateral mastectomy
Discrepancies in Variant Classification Between 9 Laboratories

Concordance of Variant Classification for BRCA1 and BRCA2

<table>
<thead>
<tr>
<th>Concordance</th>
<th>ClinVar</th>
<th>GeneDx</th>
<th>Invitae</th>
<th>Ambry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant—identical classification</td>
<td>73.2%</td>
<td>81.5%</td>
<td>85.4%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Partially concordant—multiple classifications with ≥1 concordant</td>
<td>12.3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discordant—opposite classification</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Discordant—RL uncertain classification</td>
<td>0.3%</td>
<td>0.7%</td>
<td>0.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Discordant—DB uncertain classification</td>
<td>14.0%</td>
<td>17.7%</td>
<td>13.8%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Proportion of VUSs with a definitive RL classification</td>
<td>—</td>
<td>42.5%</td>
<td>63.2%</td>
<td>56.9%</td>
</tr>
</tbody>
</table>

(322/757) (151/239) (58/102)

Abbreviations: —, not applicable; DB, database; RL, reference laboratory; VUS, variant of uncertain significance.
BRCA1 and BRCA2 are two of the most well studied genes in the Human Genome...

AND WERE EVEN SCREWING THOSE UP!

Also Keep in mind the people classifying these variants are the “experts” not general practice physicians
Elisha Cooke-Moore vs Curry County Health

Bilateral mastectomy and hysterectomy based on Incorrect interpretation of a genetic testing report by clinician

1.8 Million dollar lawsuit
The discordance in variant classification we have now is primarily based on testing done on people with disease. When you start testing healthy people it’s a completely different ball game!
Exome Sequencing

Now a common clinical test
Reports on the expressed portion of the human genome
Generates data on all your expressed genes
Resulting data is 6-8 Gigabytes of crucial health information

What does the physician get?
Genomic Data Life Cycle

Sequencing is performed on one individual
Exome generates 6 to 8 GB of data
Whole genome generates 100 to 200 GB of data
Data is processed to produce a list of candidate genes changes
Further refined to a list of reportable variants put into a PDF
So what happens to the other 6GB to 200GB of data?
MRI Analogy

VS
PACS System for Genomics

Data is too large for EHR data structures
Different kind of data requires a specialized viewer
Frequently changes – new data added
Requires specialist interpretation
May be useful for any physician to view especially at point of care
Integration of genomic data into the EMR for patient management and decision support is crucial to enabling general practice physicians to practice genomic medicine.
Summary of Challenges

• No way to store genetic data
• Clinical Genetics workforce will not scale to handle sequencing everyone
• No way to utilize genetic data in a clinical workflow
• Clinicians outside genomics not equipped to manage genetic testing results
Genetic Data – What to Store

1. Discrete Variants with Known Health Related Effects
   1. Point Mutations, Indels
   2. Copy Number Variants

2. Filtered Data
   1. VCF

3. Raw Data
   1. BAM, FastQ
Genetic Data – Where to Store

1. In EHR
2. In External Database linked to EHR
Discrete Variants

Currently reported as in a PDF
Workarounds include creating lab values that store variants
Only in past year has ability to store discrete variants been available
Getting Genetic Variants into the EHR

Epic has recently implemented “Genomic Indicators”
Will allow for clinical decision support around genomic variants
Gives genomics a home in the EHR – finally a place to put the data
Consortium for Agile Genomics – Getting Data From The Lab
HOLD UP!!!!

PDF from the lab ok to put into the system automatically
Discrete variant information as a genomic indicator – NOT OK
Why?
Bad Things Can and DO Happen

Case
• Patient in her 20s evaluated for connective tissue disease
• Clinically evaluated as hypermobile EDS
• Aortopathy panel sent
• VUS in gene for Loeys Dietz
• Cardiac MRI normal
Case – continued

- Patient seen by Ob/Gyn provider
  - Provider sees genetic test
  - Assigns diagnosis of Loeys Dietz in Epic
  - Patient instructed that she MUST have a C-section
  - Schedules monthly echocardiogram
- Patient calls genetics department
Providing too much information or too little...

Providing information that could be used the wrong way potentially exposes the patient to unnecessary and potentially harmful action.

Hiding potentially useful information prevents patient from receiving the appropriate action.

Where is the balance?
If malpractice is any indication...

Only a handful of cases regarding taking action because of wrong interpretation.

Versus....

57% of all genomic medical malpractice cases could have been avoided if genetic testing had been performed.
Pharmacogenomics

New clinical exome laboratory offers PGx variants as option to patient.
General response - Yay!
My response – Uh Oh!

Multiple patients with pharmacogenomic results
• Who counsels the patient
• Is there a liability associated with not acting on results
• How do physicians find the report?
The rest of the DATA!

Which data is used?
- Raw Data
- Filtered Data
- Annotated Data
- Copy number call from exome/genome
Storing – “The rest of the data”

No place to store VCF files
No place to store discrete phenotypic information

A Genotype- Phenotype Archiving and Communication System (GPACS)
NIH SBIR grant in partnership with PhenoSolve (SimulConsult)
Grant Number NIH 1R43HG010322-01, PI: Segal, MM
Phenotype Builder

Extracts phenotypic elements from free text and ICD10 codes
Builds phenotypic profile of HPO terms
Stores HPO terms in GPACS
We Have Genetic Data in the EHR – Now What?

Make sure genetic data is used accurately/effectively

• Diagnosis
• Clinical Decision Support
• Information Delivery to Providers
• Information Delivery to Patients
• Take Actions
Use of Genomic Information in Clinic - Simulconsult
eMERGE PGx

Clinical Decision Support built for
- CYP2C19 and Clopidogrel
- SLCO1B1 and Simvastatin
Delivering Information to Patients and Providers

- Working with Epic to implement this with genomic indicators
- Infobutton will reside next to the genomic indicator
- Provides information related to gene or variant
Compass/Gene Report

- HL7 compliant web service
- Activated through InfoButtons or direct web-link
- Delivers different information based on user - patient vs provider
- Delivers information specific to variant, sex, and age
Implementation of Chatbots

Partnership with Clear Genetics

Use Chatbots for:
- Consenting patients
- Following up on test results
- Patient questions
- Cascade testing

Chatbot work by Amy Sturm and Tara Schmidlen
Consent Chatbot

Hello, Good morning!
I'm GIA, your computer-automated Genetic Information Assistant.
I'm here to tell you about the MyCode Community Health Initiative.

MyCode is a research project that will help us learn more about human health and disease to find better ways to keep people healthy and help them when they are sick.
MyCode is using DNA testing to find patients at increased risk for things like cancer and heart disease.
Patients at increased risk can take preventative measures to lower disease risk and improve health.

Interesting, tell me more!  No thanks, I'm not interested
Patient Follow-Up Chatbot

Geisinger mycode

Geisinger follows up on all patients with MyCode results. Our computer-automated Genetic Information Assistant will ask you a few quick questions. This is to help you get the best care and to help our research.

(Chat takes 4 - 8 min)

Verify Your Information

Date of Birth (MM/DD/YYYY)

Month - Day - Year

Phone Number

(123) 456-7890

Submit

Great! As you remember, we discussed three important next steps:

1. See a provider
2. Learn more about your family health history
3. Share results with family members

Were you able to schedule an appointment regarding this genetic result?

Yes, I already had my appointment
Family Sharing Tool

You can use different sharing options for different family members and add your own note. If you're not ready to share with everyone now, come back anytime using the link you received.

- Share by Email
- Share by Text
- Share by Messenger
- Copy Link

Send a Message

To: [Enter friends]
Cc/Bcc: 
Subject: My Genetic Testing Results
I recently had genetic testing and learned that I have a gene change that may affect my health. Because we are blood relatives and share genetics, this result could impact you too. Please click the link below to learn more about what this means and what you can do.

https://app.cleargenetics.com/invite/x5a8d430dbe7a5/share

Genetic Information Sharing Tool

Family members share genetics. So it only makes sense that we should also share information about our genetics. Let's start the domino effect of improved care based on genetic information.

APP.CLEARGENETICS.COM

Terms and Conditions
Cascade Chatbot

Jane is in a genetic study at Geisinger, a health system in Pennsylvania. She learned information about her health that could impact you. GIA, a computer-automated Genetic Information Assistant, will provide more details.

(Chat takes 2-5 min)

We recently learned that Jane has a gene change that keeps her LDLR gene from working correctly.

When the LDLR gene doesn't work, people are at increased risk for Familial Hypercholesterolemia (FH), which is associated with early heart attack and stroke from inherited high cholesterol.

This gene change usually runs in families and is passed down from parents to children.

Tell us if your LDLH gene works or doesn't work.

What if my gene also doesn't work?

If your gene also doesn't work, then you too may have an increased risk for Familial Hypercholesterolemia (FH), which is associated with early heart attack and stroke from inherited high cholesterol.

There may be steps that you can take to detect early or even prevent high cholesterol.
Smart FAQ
What’s Next?

• How do we integrate all genomic information into the workflow?
• Which variants do we include and who decides?
• When working outside an "expert" whose consensus guidelines are used?
• How can we effectively use information in real-time to impact patient care?
Acknowledgements

Geisinger
- Marc Williams
- Darren Johnson
- Bruce Levy
- Dean Parry
- Jordan Olson
- Bonnie Spandra
- Rebecca Pulk
- Chancey Christenson
- Amy Sturm
- Tara Schmidlen

University of Nebraska
- Scott McGrath

Simulconsult
- Michael Segal
- Lynn Feldman

HPO
- Peter Robinson

Epic
- Jordan Dantas

InfoButtons
- Guilherme Del Fiol

HL7/FHIR
- Gil Alterovitz
- Grant Wood
QUESTIONS?