Lessons from a Genomic Screening Program

Mike Murray, MD
Geisinger Genomic Medicine Institute

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NCI Webinar:
Integrating Genome Sequencing in Health Care Systems:
Evaluation, Implementation and Population Health Impact
Disclosure

Dr. Murray reports consulting for InVitae and Merck, and grant funding from Regeneron.

Dr. Murray reports no intellectual property claims related to this work.

No conflicts of interest related to this presentation.
Categories of Results to consider returning to patients who get “screening” DNA sequencing in February 2018 include:

1. Carrier status
2. Pharmacogenomics
3. Polygenic Risk scores
4. Monogenic results
Geisinger Monogenic Variant Return started in May 2015

https://go.geisinger.org/results
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What made Geisinger the place to start delivering Monogenic Risk Results in 2015?

1. Integrated Health Care System
2. Appropriately Consented Biobank of Patient-Participants
3. Research Collaboration with BioPharma Company
4. Mature EHR environment
5. Focused Institutional Commitment
The MyCode Community Health Initiative (Initiated 2007)

Currently > 175,000 Participants

Inclusion Criteria = “Geisinger Patient”
“Scientifically and medically, it’s pretty exciting,” said Dr. Leslie G. Biesecker, chief of the genetic disease research branch at the government’s National Human Genome Research Institute, who is familiar with the project.

“As far as I’m aware, it’s the largest clinical sequencing undertaking in this country so far by a long shot.”

He added that the move of sequencing into general health care “is going to change medicine.”
The DiscovEHR Study and its Goals

Primary Objective is Discovery Research (Geisinger and Regeneron)

Secondary Objective is Return of Results to Patient Care (Geisinger)

From the research data secondary results are:
- Identified
- Clinically confirmed
- Placed in EHR
- Follow-up is supported
## Elements of the Infrastructure Built, Enhanced, or Under Development for Genomic Return of Results

| TABLE 1. RESOURCES DEVELOPED TO SUPPORT CLINICAL RETURN OF GENOMIC RESULTS |
|-----------------------------|-----------------------------|-----------------------------|
| Resource                        | Description                                      | Supports                      |
| Clinical Genomics Team         | Includes national leaders in genomic medicine –  medical geneticists, genetic counselors, physician extenders and pharmacists | Patients, families, clinicians |
| Oversight Committees           | Infrastructure and care management is routinely evaluated by IRB, Clinical Oversight, Ethical Oversight, and Genomics Oversight Committees composed of experts and patients | Patients, families, clinicians |
| Telemedicine Visits            | Improves patients' access to Clinical Genomics team across our large geographic catchment area | Patients, families, clinicians |
| Condition-Specific Multi-Disciplinary Clinics | Helps patients and clinicians efficiently develop a multi-disciplinary care plan (e.g. HBOC and Lynch Syndrome programs). | Patients, families, clinicians |
| Family History Tool            | Patient-entered, electronic tool that guides targeted collection of family history; allowing for patient assessment and prioritization of familial cascade testing | Patients, families, clinicians |
| Patient-Centered Genomic Reports | Describes genomic change, risk management recommendations and support resources in lay language | Patients, families, clinicians |
| Condition-Specific Educational Modules | Online CME modules with review of relevant details related to evaluation and management of a person receiving a specific incidental genomic findings | Clinicians |
| Electronic Health Record (EHR) Tools | Guide clinicians in evaluation for genomic condition symptoms, development of risk management plan, and EHR documentation via smart sets. | Clinicians |
| Provider Liaison               | Communicates with and assists providers outside of Geisinger who are caring for a GenomeFIRST patient. Usually those providers belong to primary care practices who have referred patients to specialty care at GHS. | Clinicians |
| Cascade Testing Facilitator    | Communicate with patients, families, and providers. Facilitates insurance prior authorizations and ensures laboratory receipt of correct variant data. | Patients, families, Clinicians |
Geisinger’s Return of Genomic Results

Three Essential Steps Once Result Delivered to Care

1. Communication and Counseling
2. Condition specific evaluation and management
3. Cascade testing of at-risk relatives
Five Diagnostic Groups for Incidental Findings Cases

- **GROUP 1**: Previous Clinical Genetic Testing
  - Genotype + Phenotype +

- **GROUP 2**: No Previous Clinical Genetic Testing
  - Genotype + Phenotype +

- **GROUP 3**: Sub-critical Phenotype Revealed Thru ROR Evaluation
  - Genotype + Phenotype +

- **GROUP 4**: Phenotype Emerges Over Time
  - Genotype + Phenotype – to +

- **GROUP 5**: Phenotype Does Not Emerge
  - Genotype + Phenotype -

- **GENE SPECIFIC EVALUATION Including History, Exam, Testing, Consultation**

- **GENOMIC SYNDROME DIAGNOSED**

"Your DNA is Not Your Diagnosis"
Murray Genet Med. 2016 Aug
Five Diagnostic Groups for Incidental Findings Cases

Secondary Or Incidental Finding Of A Pathogenic/Likely Pathogenic Variant

GENE SPECIFIC EVALUATION Including History, Exam, Testing, Consultation

GROUP 1
Previous Clinical Genetic Testing
Genotype + Phenotype +

GROUP 2
No Previous Clinical Genetic Testing
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GENOMIC SYNDROME DIAGNOSED

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PRIORITIES and PREVALENCE
Three “Public Health Tier One” conditions will drive return of results for > 1:80 (1.25%) of participants

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<th>Three Tier One CONDITIONS</th>
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<th>DISEASE-ALTERING INTERVENTION</th>
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<td>Targeted screening and medical management</td>
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<td>TOTAL</td>
<td>670</td>
<td><strong>1:76 (1.32%)</strong></td>
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Newborn Screening delivers a positive result to ~1:800

~150,000 people in the State of Pennsylvania (population 12.8M)
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| PARTICIPANTS WITH RISK VARIANT IN 50,726 ADULTS IN THE MYCODE COHORT |
|-------------------------------------------------|---------------------------------------------------|--------------------------------|
| CONDITION            | NUMBER OF VARIANT CARRIERS | PREVALENCE OF “GENOMIC SCREEN” POSITIVE | PUBLISHED PREVALENCE ESTIMATES |
| FH                  | 229                        | 1:222                                    | 1:500                         |
| HBOC                | 268                        | 1:189                                    | 1:400                         |
| LS                  | 173                        | 1:293                                    | 1:440                         |
| TOTAL               | 670                        | 1:76 (1.32%)                             | 1:148                         |

Newborn Screening delivers a positive result to ~1:800

~150,000 people in the State of Pennsylvania (population 12.8M)
How are Health Systems doing at identifying these risks without Genomic Screening?
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BRCA 1/2 Cases

- Prior Clinical Testing: 20%
- No Prior Clinical Testing: 80%
How are Health Systems doing at identifying these risks without Genomic Screening?

- Prior Clinical Testing: 20%
- No Prior Clinical Testing, Meets Criteria for Testing: 40%
- No Prior Clinical Testing, Does Not Meet Criteria for Testing: 40%
Genomic Screening Makes Invisible Risks Visible

BRCA 1

57 year-old grandmother bringing up three grandchildren ages 3, 5, and 14 y.o.

When found to have a pathogenic variant she said, “Okay, so what do we do next? I have 15 more years to go until they’re raised.”

No personal or family history

Genetic Follow-up
- Negative mammogram
- Elected to have preventive bilateral salpingo-oophorectomy
- Stage 1 fallopian tube cancer
- Excellent Prognosis
- Daughter tested for +BRCA1
Genomic Screening Makes Invisible Risks Visible

Familial Hypercholesterolemia

![Graph showing maximum EHR-documented LDL-C (mg/dl) for FH variant negative and positive.]

![Bar chart showing data ratio for coronary artery disease (CAD) in different LDL cholesterol categories.]

Correcting Misattribution Possible and it Matters
Cardiac Hypertrophy Prior to Results (N=14)

Mean age at diagnosis
46 y (range 27-62y)

Obstructive HCM (14.29%)
Non-Obstructive HCM (21.43%)
Hypertensive Heart Disease (14.29%)
None Documented (50%)
Congestive Heart Failure
Correcting Misattribution Possible and it Matters
Cardiac Hypertrophy Following Results (N=14)

Mean age currently 55 y (range 30-83y)
Cascade Testing Extends the Reach

MyCode ROR Reach – Beyond Geisinger
ACKNOWLEDGEMENTS

• Patient-Participants
• Geisinger Health System
• Regeneron Genomics Center
• Laboratory for Molecular Medicine