Caring

Geisinger

Lessons from a Genomic Screening Program

Mike Murray, MD
Geisinger Genomic Medicine Institute

November 1st 2017

Roundtable on Genomics and Precision Health

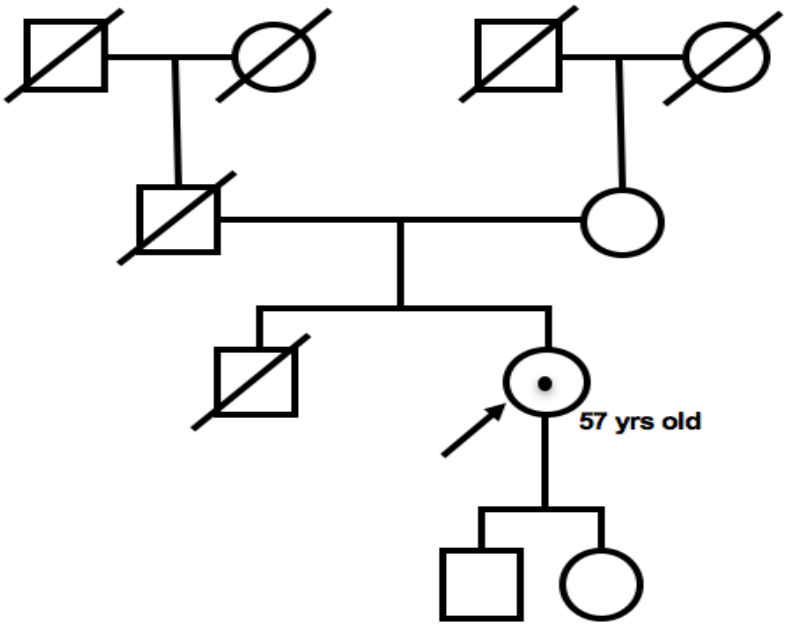
National Academy of Science

Washington DC

No Personal or Family History of Breast or Ovarian Cancer

SCIENCE | 27 OCT 2017 : 436-440

No Personal or Family History of Breast or Ovarian Cancer



***BRCA2* variant +**

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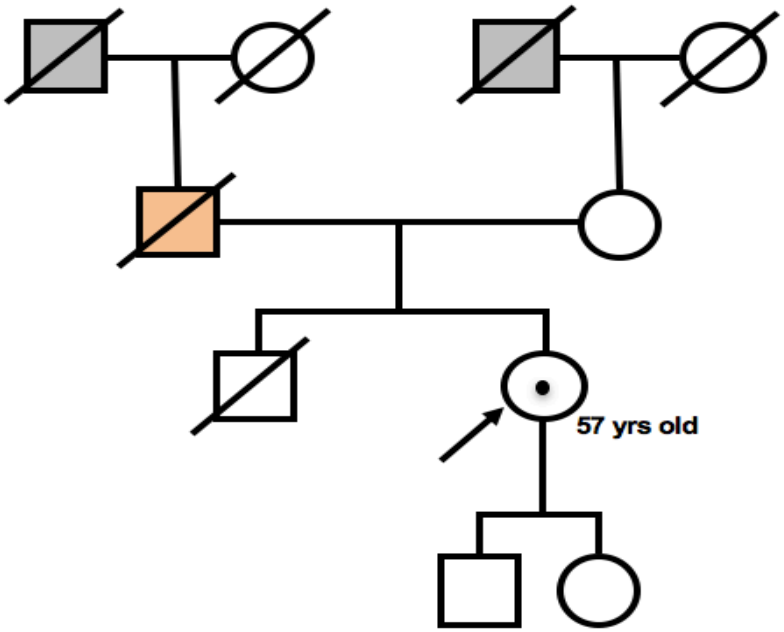

LEGEND

- Colon CA
- Lung CA
- Prostate CA
- *BRCA2* variant +

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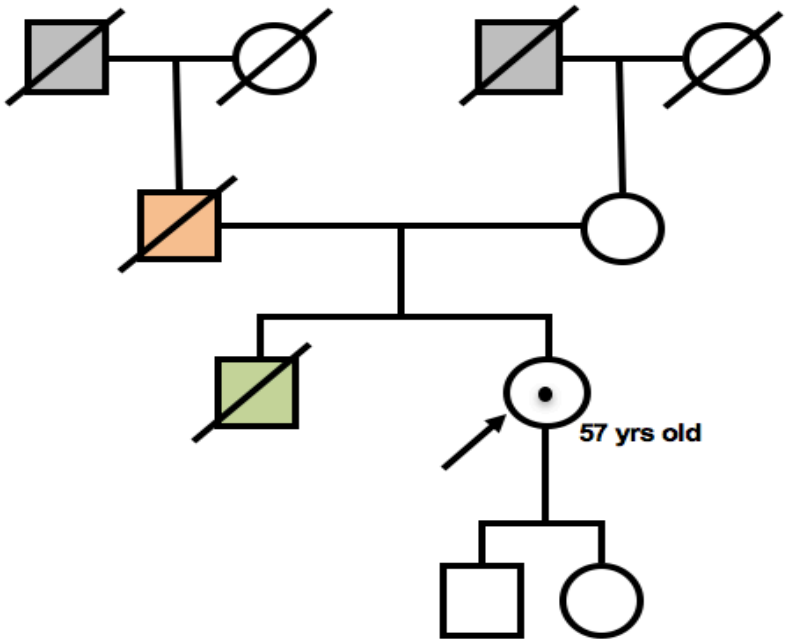

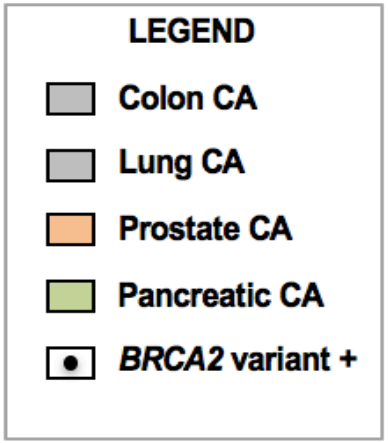

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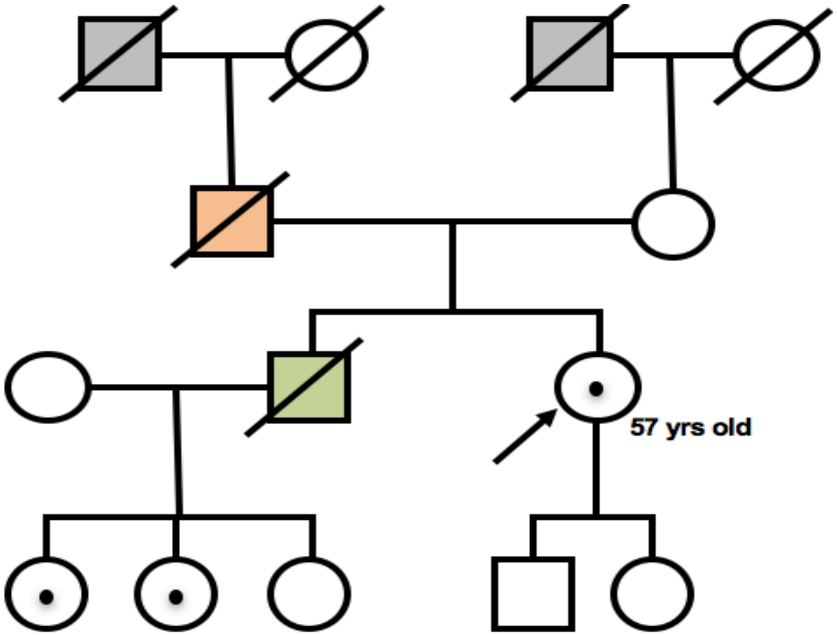

LEGEND

- Colon CA
- Lung CA
- Prostate CA
- Pancreatic CA
- *BRCA2* variant +

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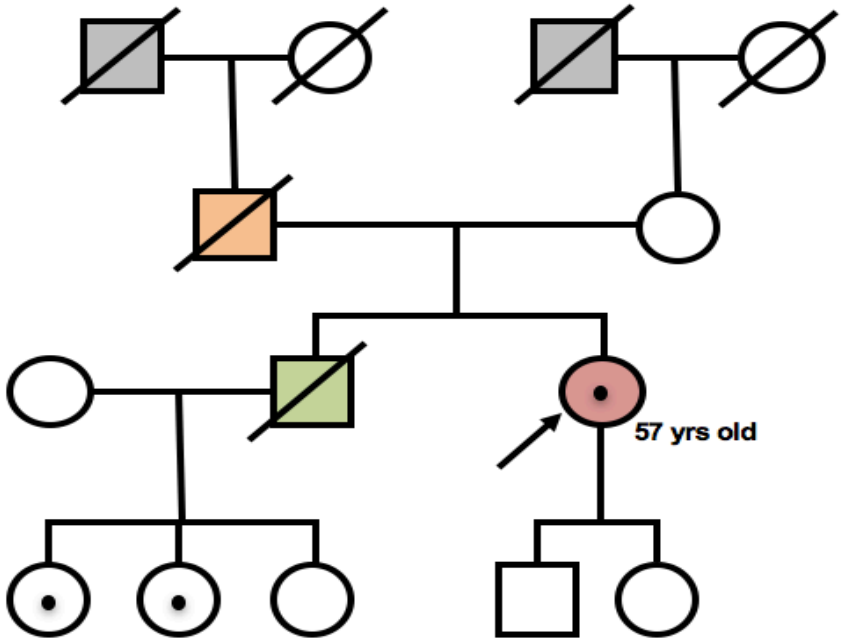
Personal History of Breast or Ovarian Cancer



LEGEND

- Colon CA
- Lung CA
- Prostate CA
- Pancreatic CA
- Breast CA
- *BRCA2* variant +

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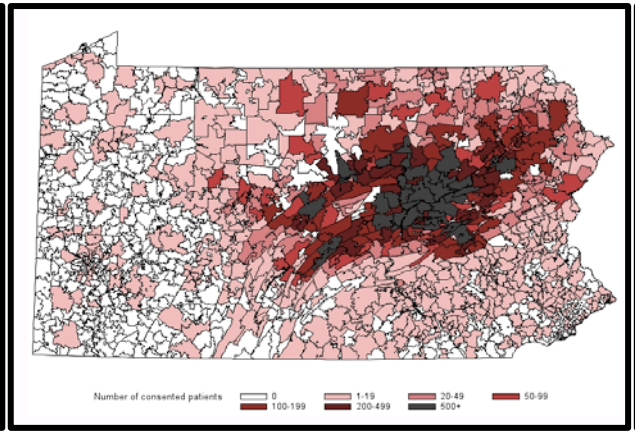
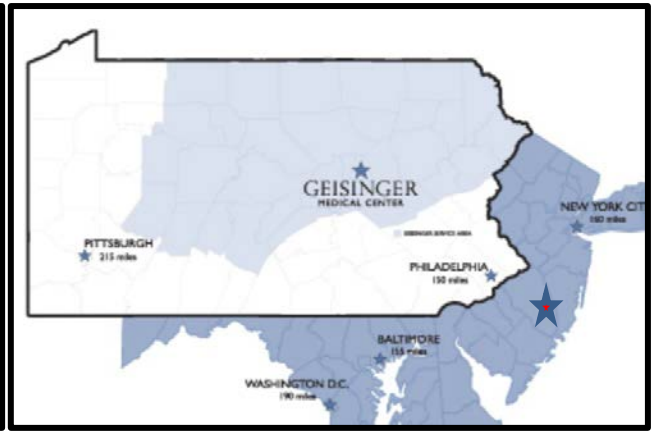
The MyCode Community Health Initiative (Initiated 2007)





Currently > 170,000 Participants

Inclusion Criteria = "Geisinger Patient"

Geisinger-Regeneron DiscovEHR Study

Geisinger-Regeneron DiscovEHR Study

The New York Times

Jan. 13, 2014

Aiming to Push Genomics Forward in New Study

By ANDREW POLLACK

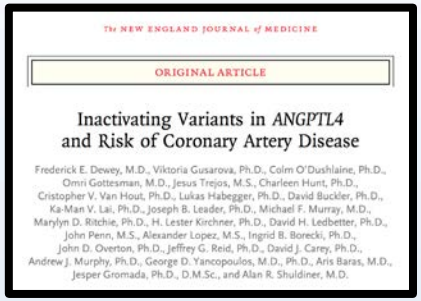
"Scientifically and medically, it's pretty exciting," said Dr. Leslie G. Biesecker, chief of the genetic disease research branch at the government's National Human Genome Research Institute, who is familiar with the project.

"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

Geisinger

Geisinger's Return of Results Program

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

Identifying and Returning Risk

https://go.geisinger.org/results

MyCode® results returned

417 patient-participants have received results*

Geisinger mycode | 150,000+ PARTICIPANTS

For the latest results, see go.geisinger.org/results.

October 1, 2017

Risk condition	Patients per risk condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)	196	BRCA1	67
		BRCA2	129
Familial hypercholesterolemia (early heart attacks and strokes)	43	APOB	17
		LDLR	26
Lynch syndrome (early colon, uterine and other cancers)	37	PMS2	15
		MSH6	14
		MSH2	5
		MLH1	3
Cardiovascular risk			
Cardiomyopathy (diseases of the heart muscle with dangerous complications)	35	MYH7	4
		MYBPC3	21
		TPM1	2
		TNNI3	1
		TNNT2	3
		MYL3	4
Arrhythmia (irregular heartbeat with risk for cardiac arrest)	26	SCN5A	16
		KCNQ1	7
		KCNE1	2
		KCNH2	1
Arrhythmogenic right ventricular cardiomyopathy (disease of the heart muscle with risk for cardiac arrest)	18	DSP	6
		PKP2	11
		DSG2	1
Marfan syndrome (connective tissue disease that can cause heart, eye, and skeletal problems)	3	FBN1	3
Heritable thoracic aortic disease (genetic predisposition to weakening of the wall of the aorta, leading to swelling and sometimes rupture)	9	ACTA2	9

(continued on next page)

MyCode® results returned

417 patient-participants have received results* (continued)

October 1, 2017

Risk Condition	Patients per risk condition	Gene	Patients per gene
Cancer risk			
Hereditary pheochromocytomas and paragangliomas (specific tumors that can release extra hormones)	9	SDHB	3
		SDHC	3
		SDHD	3
Multiple endocrine neoplasia type 1 (early thyroid cancer)	5	MEN1	5
Multiple endocrine neoplasia type 2 (early thyroid cancer)	12	RET	12
PTEN hamartoma tumor syndrome (characterized by noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers as well as intellectual disability in some cases)	3	PTEN	3
Tuberous sclerosis (multiple types of benign [non-cancer] tumors)	1	TSC2	1
Li-Fraumeni syndrome (early breast, soft tissue, brain, adrenal and other cancers)	5	TP53	5
Familial adenomatous polyposis (early colon cancer)	1	APC	1
Other			
Malignant hyperthermia (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)	16	RYR1	16
Fabry disease (enzyme defect leading to damage of blood vessels in the skin and cells in the kidneys, heart, and nervous system)	1	GLA	1
Totals	420		420

*Number of patient-participants with returned results and the number per gene variant/condition may not be equal due to the possibility of a participant having more than one condition.

Geisinger

https://go.geisinger.org/results

PRIORITIES and PREVALENCE

Three "Public Health Tier One" conditions will drive return of results for > 1:80 (1.25%) of participants

Three Tier One CONDITIONS	CLINICAL RISK	DISEASE-ALTERING INTERVENTION
Familial Hypercholesterolemia (FH)	Early-onset Coronary Artery Disease and Stroke	Targeted screening and medical management
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	Early-onset Breast, Ovarian, and Prostate Cancers	Targeted screening with prophylactic medical and surgical intervention
Lynch Syndrome (LS)	Early-onset Colon and Uterine Cancers	Targeted screening and management of pre-cancerous changes

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)

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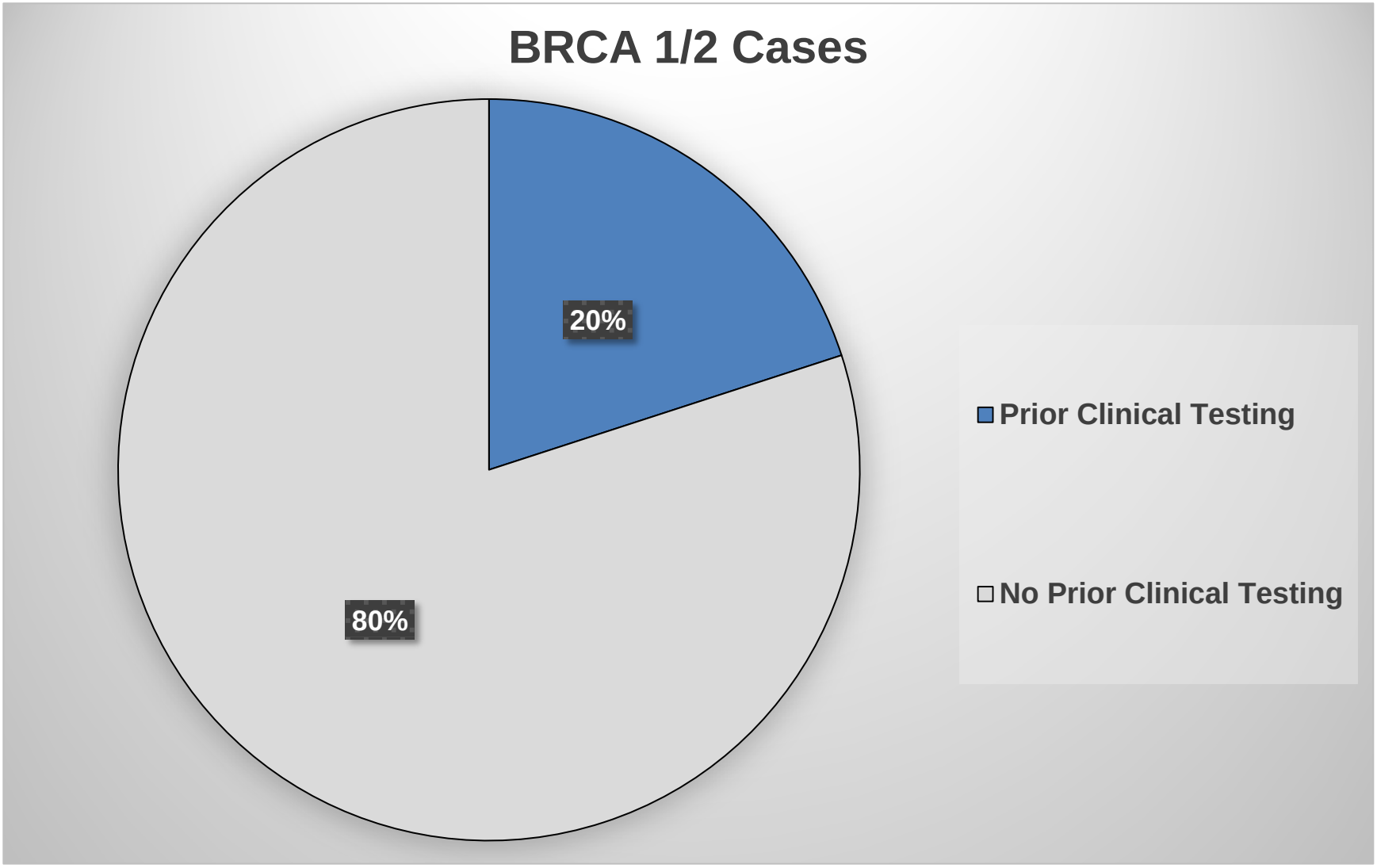

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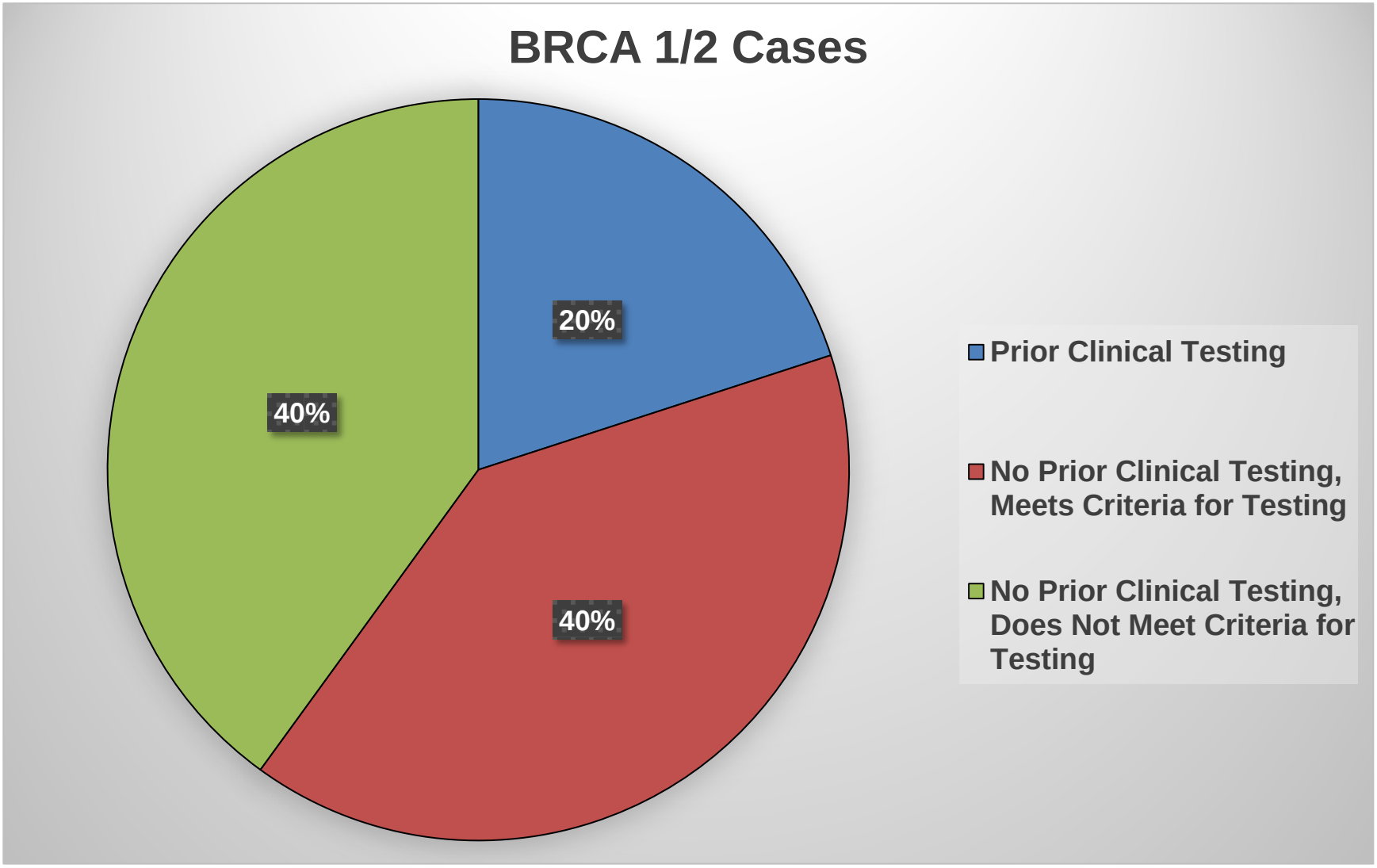


Elements of the Infrastructure Built, Enhanced, or Under Development for Genomic Return of Results

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

GENOMIC SCREENING: What Can we say?

OBSERVED

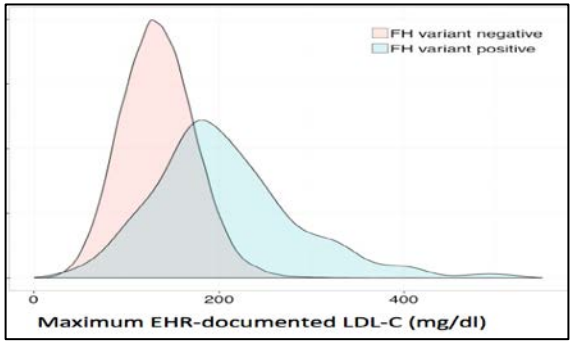
1. **Genomic Screening Makes Invisible Risks Visible**
2. **Traditional Pretest Genetic Counseling Impossible**
3. **Primary Care Providers will Defer Management**
4. **Correcting Misattribution Possible and it Matters**

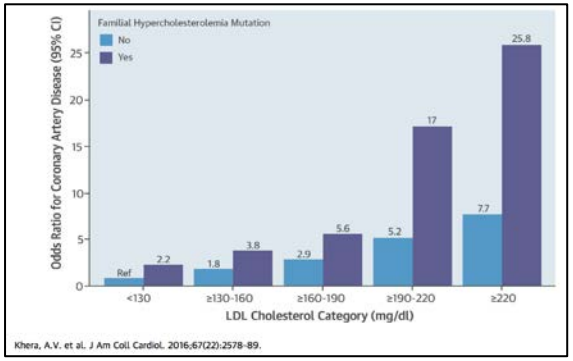
PENDING

1. We Need to Avoid False Reassurance
2. We Need to Understand Non-Penetrance
3. We Need to Make Cascade Testing Work

Genomic Screening Makes Invisible Risks Visible

Familial Hypercholesterolemia





Khera, A.V. et al. J Am Coll Cardiol. 2016;67(22):2578-89.

Genomic Screening Makes Invisible Risks Visible

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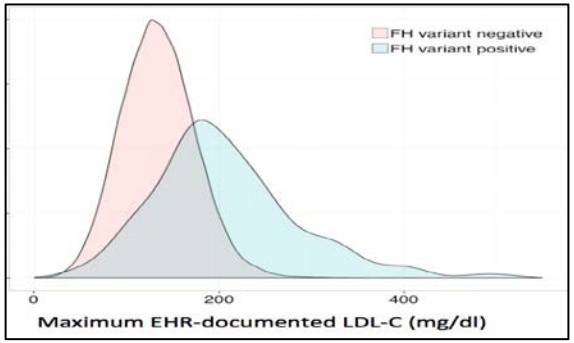

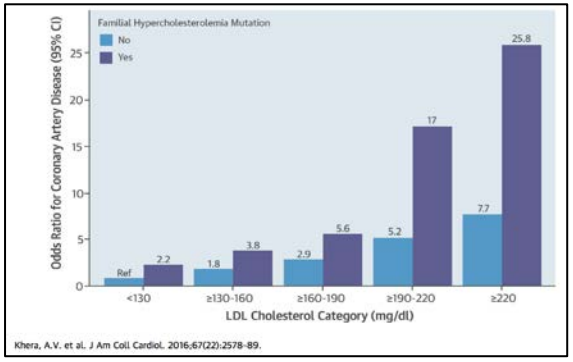

BRCA 1

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*

Traditional Pretest Genetic Counseling Impossible

RESEARCH ARTICLE

HUMAN GENETICS

Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study

SCIENCE sciencemag.org 23 DECEMBER 2016 • VOL 354 ISSUE 6319

	Variant positive/ total	Estimated prevalence
One clinically actionable genetic variant in G76	46/1415	1:31 (3.3%)
Two clinically actionable genetic variants in G76	3/1415	1:472 (0.2%)
Total	**49/1415**	**1:29 (3.5%)**

Primary Care Providers will Defer Management

Initial Experience

270 provider notifications

- 187 internal PCPs
- 76 external PCPs
- 53 internal provider of record
- 7 no PCP

184 unique provider notifications

- 84 internal PCPs
- 62 external PCPs
- 38 internal providers of record

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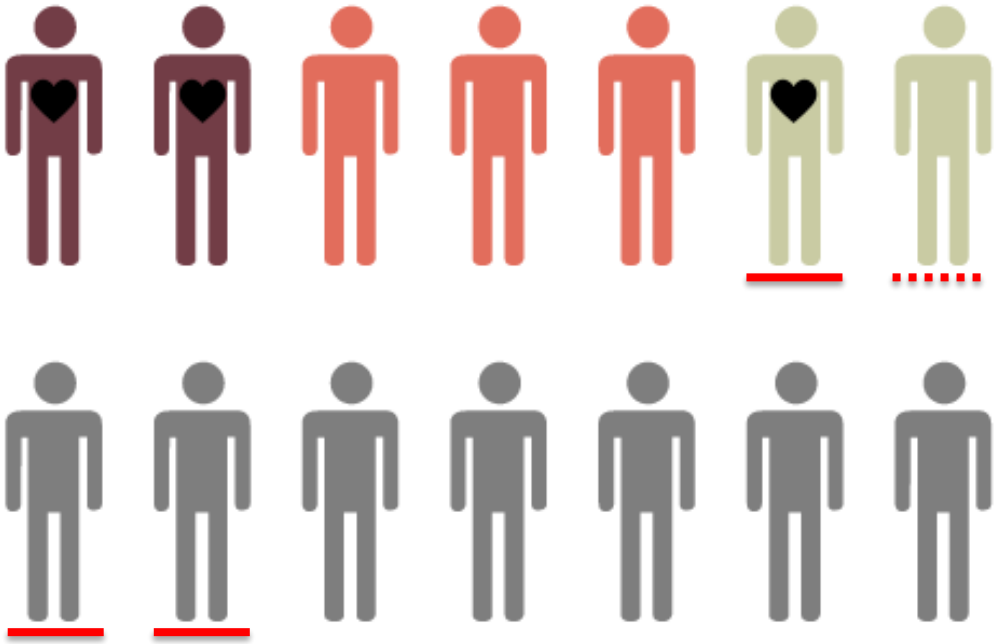
Clinical Parallels

PPD and Primary Care

Correcting Misattribution Possible and it Matters

Cardiac Hypertrophy Prior to Results (N=14)

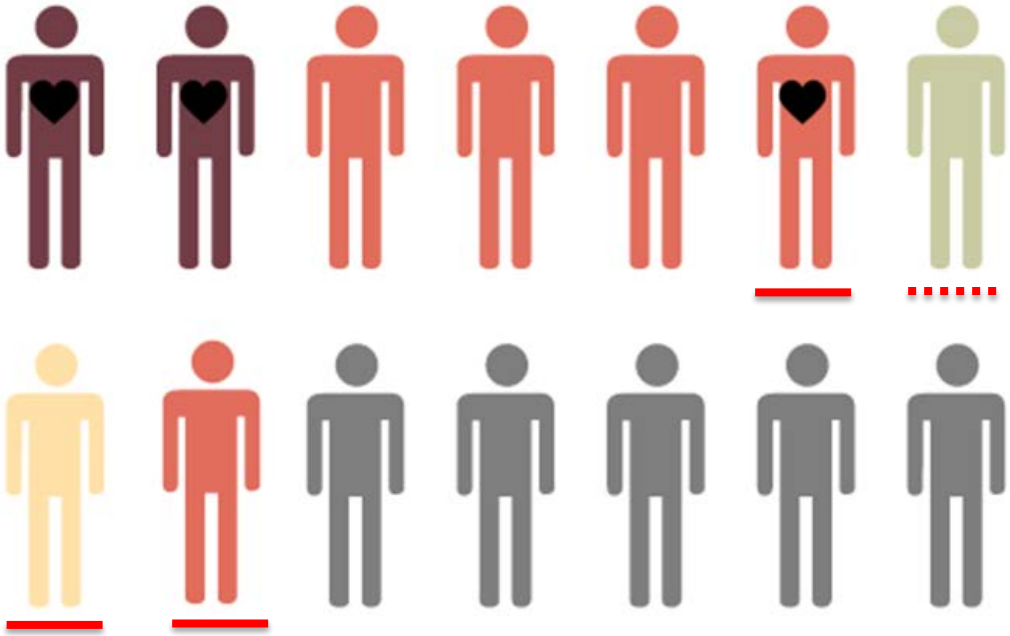


Mean age at diagnosis
46 y (range 27-62y)

- 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)

- Obstructive HCM
- Non-Obstructive HCM
- Hypertensive Heart Disease
- Concentric LVH
- None Documented
- Congestive Heart Failure

GENOMIC SCREENING: What Can we say?

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PENDING

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2. **We Need to Understand Non-Penetrance**
3. **We Need to Make Cascade Testing Work**

We Need to Avoid False Reassurance

At Geisinger

- **No result = no result**
- **If clinically indicated test then don’t join MyCode to get it done.**

We Need to Understand Non-Penetrance

We cannot currently distinguish

- **those without disease who will eventually develop it**

from

- **those without disease who will never develop it**

We Need to Make Cascade Testing Work

MyCode ROR Reach – Beyond Geisinger

ACKNOWLEDGEMENTS

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