Caring

Geisinger

Lessons from a Genomic Screening Program

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Geisinger Genomic Medicine Institute

February 14th 2018

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.

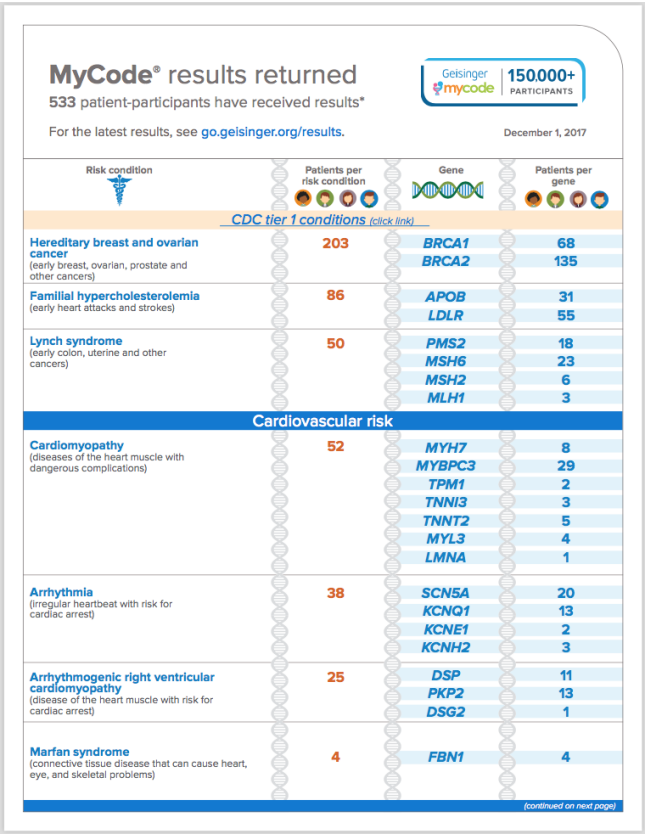
Categories of Results **to consider returning to patients who get "screening" DNA sequencing in February 2018 include:**

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

Geisinger Monogenic Variant Return started in May 2015



MyCode® results returned

533 patient-participants have received results*

Geisinger mycode 150,000+ PARTICIPANTS

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

December 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)	203	BRCA1	68
		BRCA2	135
Familial hypercholesterolemia (early heart attacks and strokes)	86	APOB	31
		LDLR	55
Lynch syndrome (early colon, uterine and other cancers)	50	PMS2	18
		MSH6	23
		MSH2	6
		MLH1	3
Cardiovascular risk			
Cardiomyopathy (diseases of the heart muscle with dangerous complications)	52	MYH7	8
		MYBPC3	29
		TPM1	2
		TNNI3	3
		TNNT2	5
		MYL3	4
		LMNA	1
Arrhythmia (irregular heartbeat with risk for cardiac arrest)	38	SCN5A	20
		KCNQ1	13
		KCNE1	2
		KCNH2	3
Arrhythmogenic right ventricular cardiomyopathy (disease of the heart muscle with risk for cardiac arrest)	25	DSP	11
		PKP2	13
		DSG2	1
Marfan syndrome (connective tissue disease that can cause heart, eye, and skeletal problems)	4	FBN1	4

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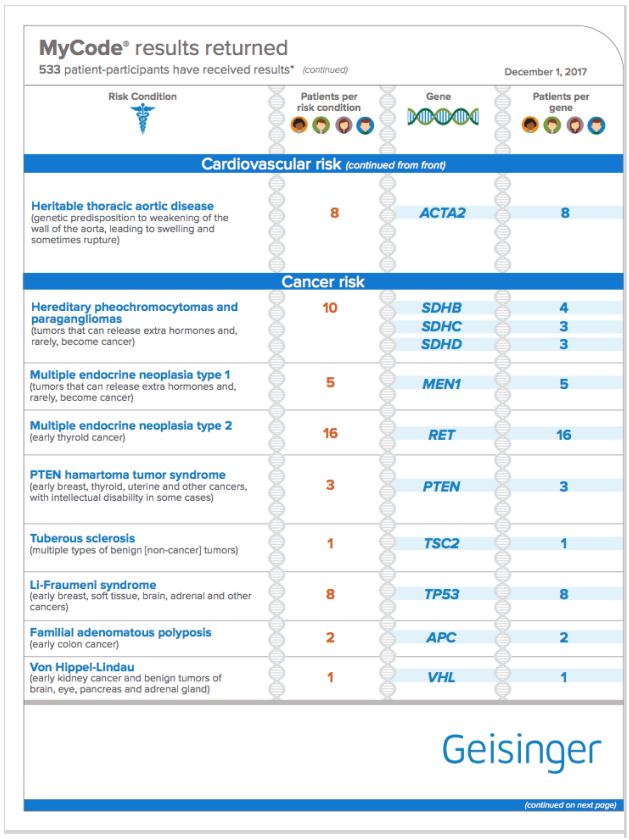

MyCode® results returned

533 patient-participants have received results* *(continued)*

December 1, 2017

Risk Condition	Patients per risk condition	Gene	Patients per gene
Cardiovascular risk *(continued from front)*			
Heritable thoracic aortic disease (genetic predisposition to weakening of the wall of the aorta, leading to swelling and sometimes rupture)	8	ACTA2	8
Cancer risk			
Hereditary pheochromocytomas and paragangliomas (tumors that can release extra hormones and, rarely, become cancer)	10	SDHB	4
		SDHC	3
		SDHD	3
Multiple endocrine neoplasia type 1 (tumors that can release extra hormones and, rarely, become cancer)	5	MEN1	5
Multiple endocrine neoplasia type 2 (early thyroid cancer)	16	RET	16
PTEN hamartoma tumor syndrome (early breast, thyroid, uterine and other cancers, with 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)	8	TP53	8
Familial adenomatous polyposis (early colon cancer)	2	APC	2
Von Hippel-Lindau (early kidney cancer and benign tumors of brain, eye, pancreas and adrenal gland)	1	VHL	1

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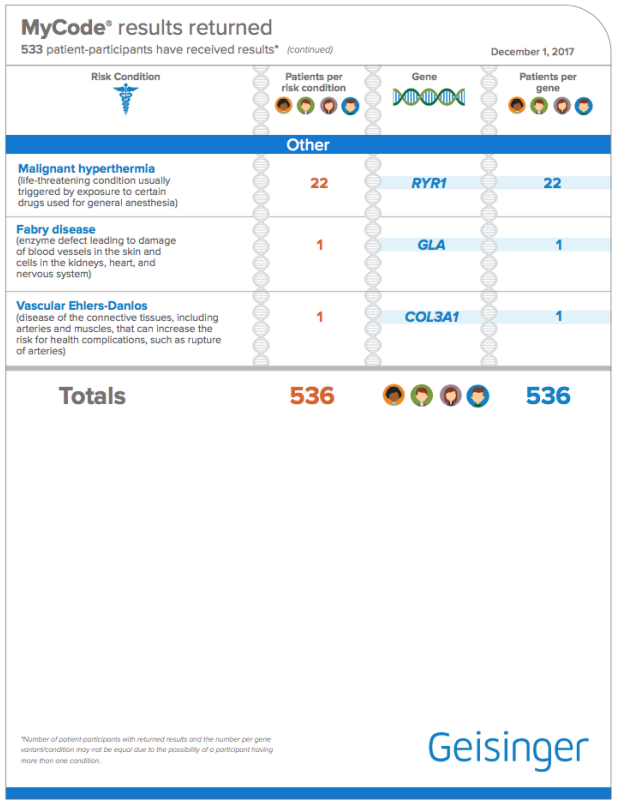

MyCode® results returned

533 patient-participants have received results* *(continued)*

December 1, 2017

Risk Condition	Patients per risk condition	Gene	Patients per gene
Other			
Malignant hyperthermia (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)	22	RYR1	22
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
Vascular Ehlers-Danlos (disease of the connective tissues, including arteries and muscles, that can increase the risk for health complications, such as rupture of arteries)	1	COL3A1	1
Totals	536		536

*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.

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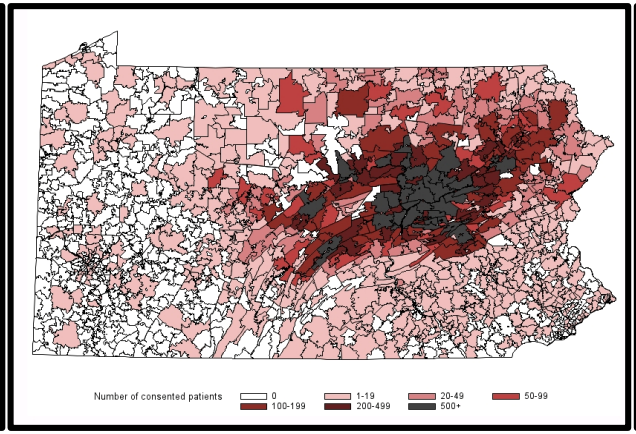
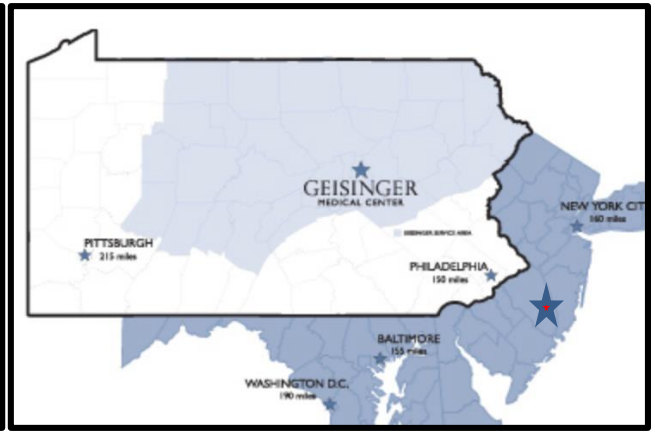
https://go.geisinger.org/results

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"

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**

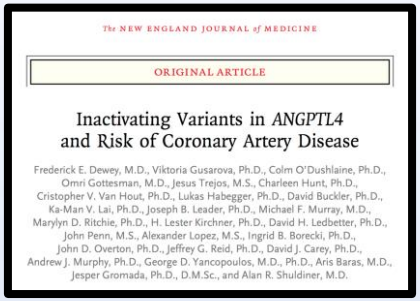
"Scientifically and medically, it's pretty exciting," said Dr. Leslie G. Biesecker, chief of the genetic disease research branch at the government's National Human Genome Research Institute, who is familiar with the project.

"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)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Variants in *ANGPTL4* and Risk of Coronary Artery Disease

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

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

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

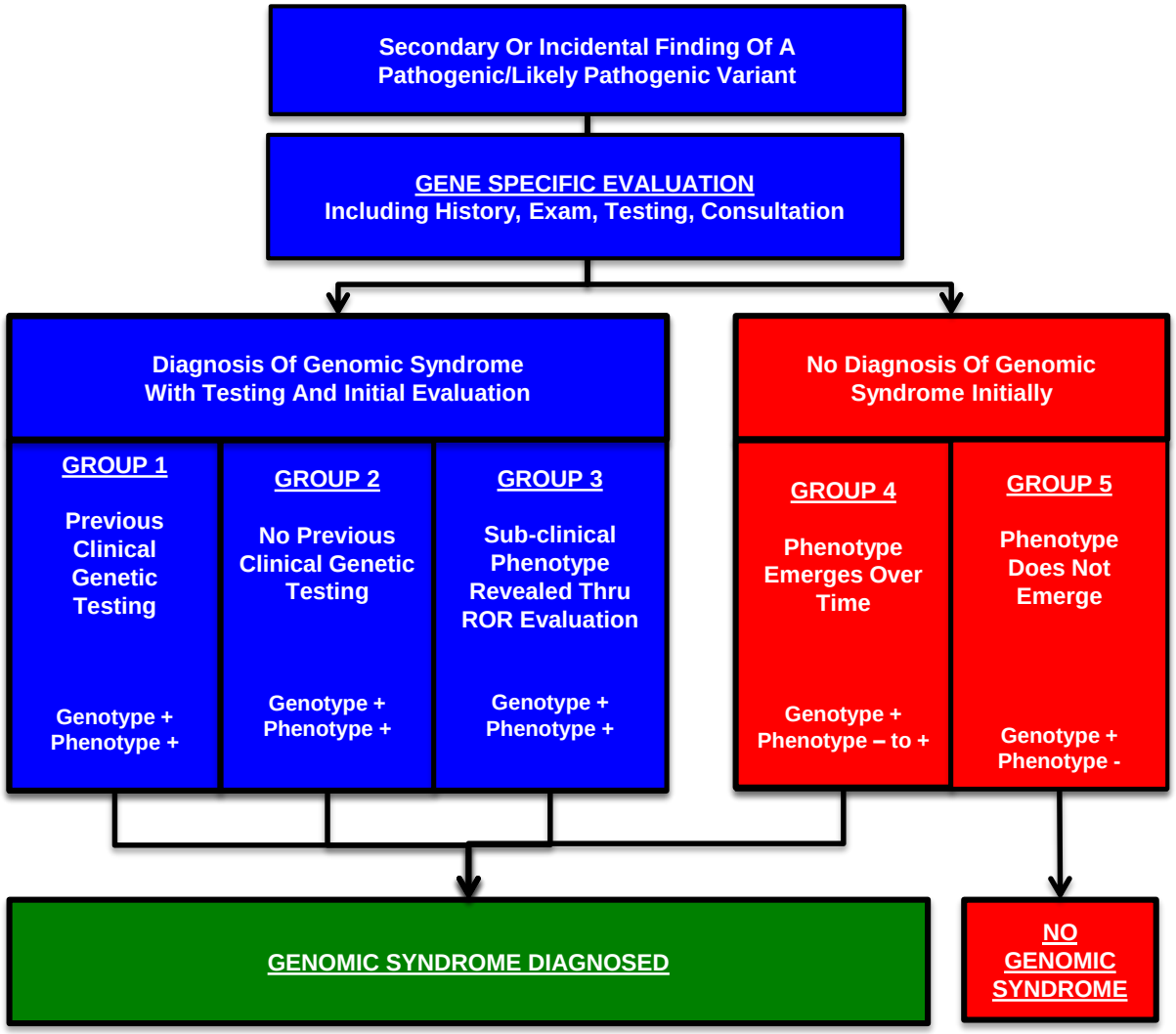
TABLE 1. RESOURCES DEVELOPED TO SUPPORT CLINICAL RETURN OF GENOMIC RESULTS		
Resource	**Description**	**Supports**
Clinical Genomics Team	Includes national leaders in genomic medicine – medical geneticists, genetic counselors, physician extenders and pharmacists	Patients, families, clinicians
Oversight 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

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



"Your DNA is Not Your Diagnosis"
Murray *Genet Med*. 2016 Aug

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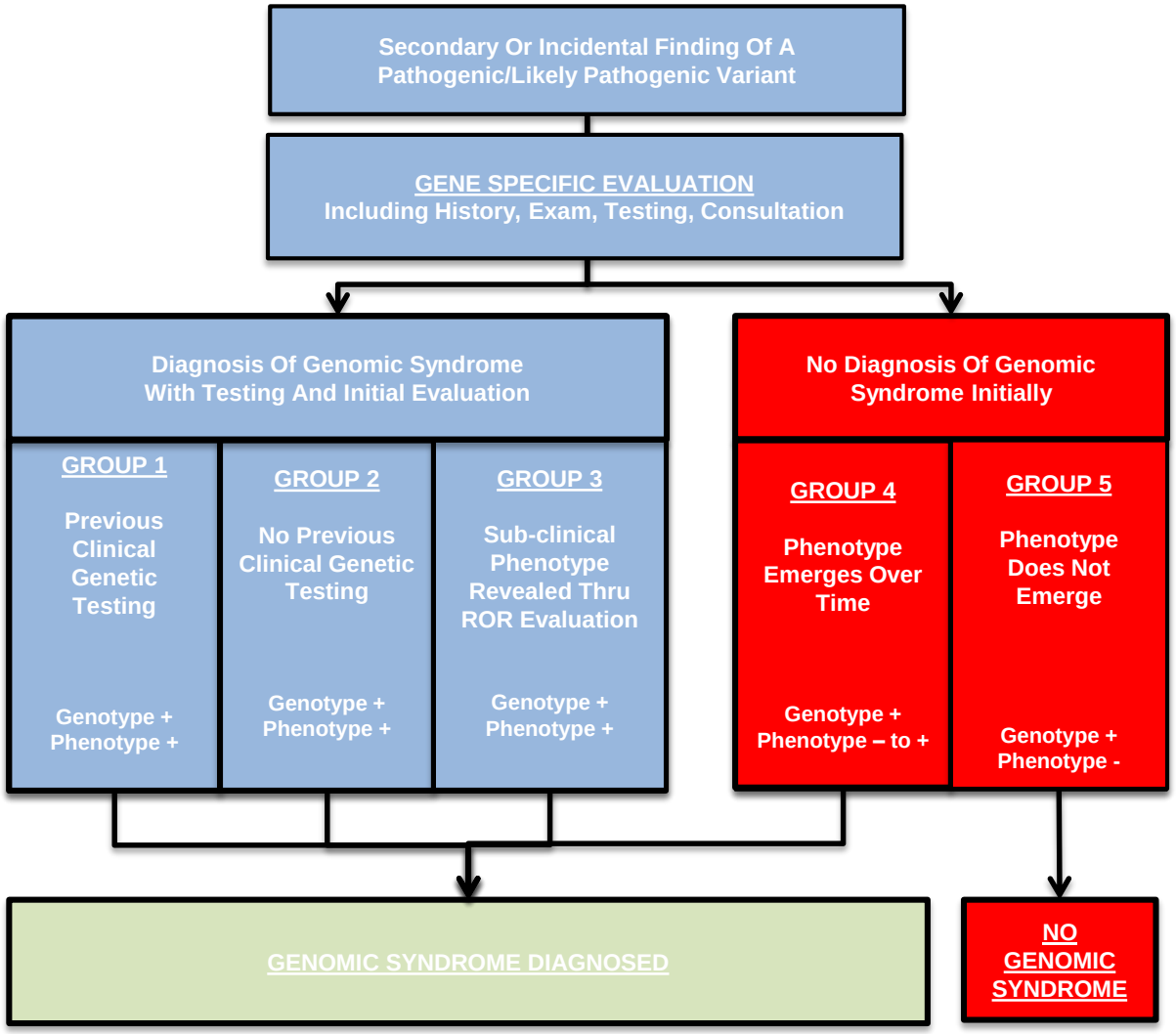

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PRIORITIES and PREVALENCE

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

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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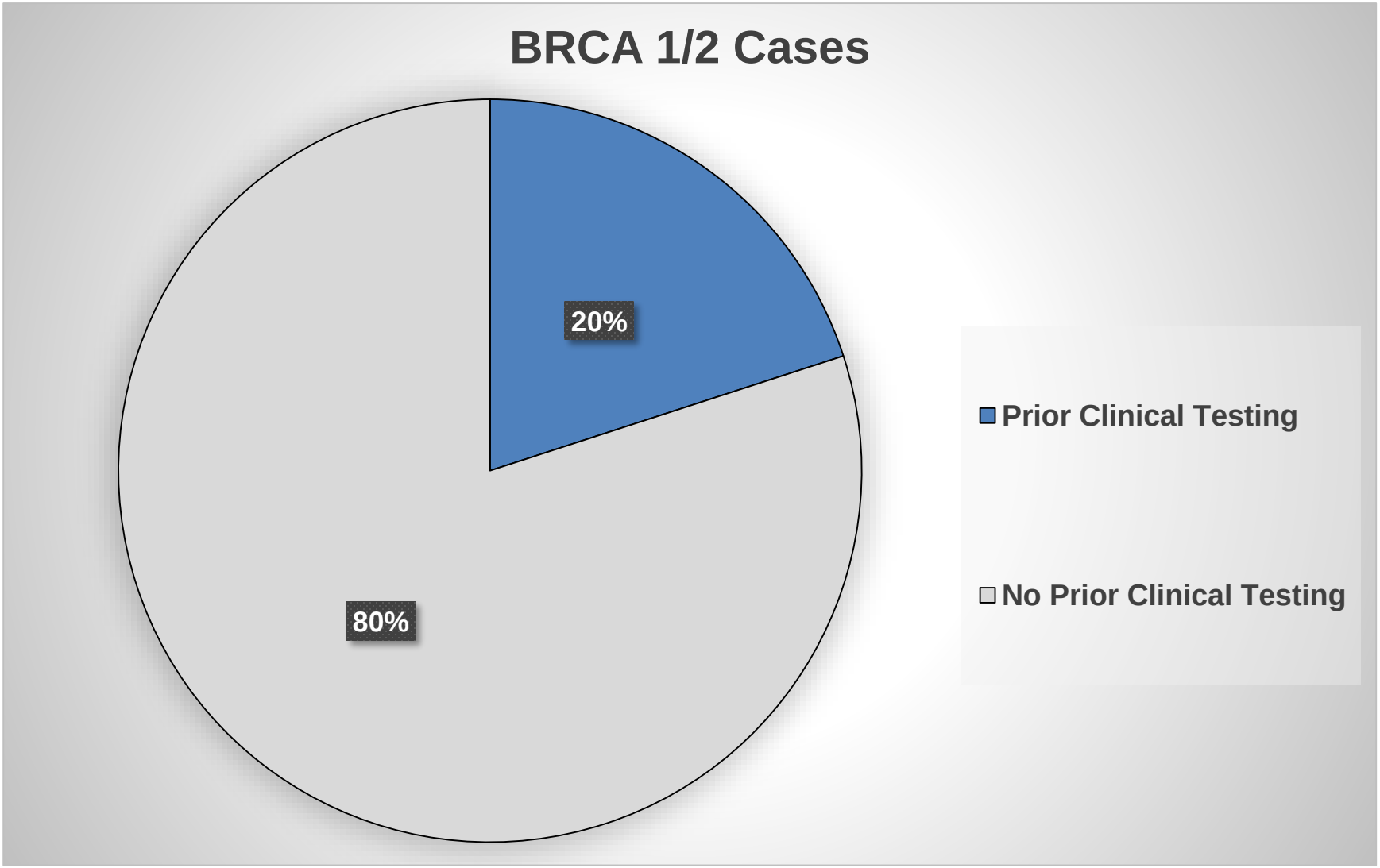

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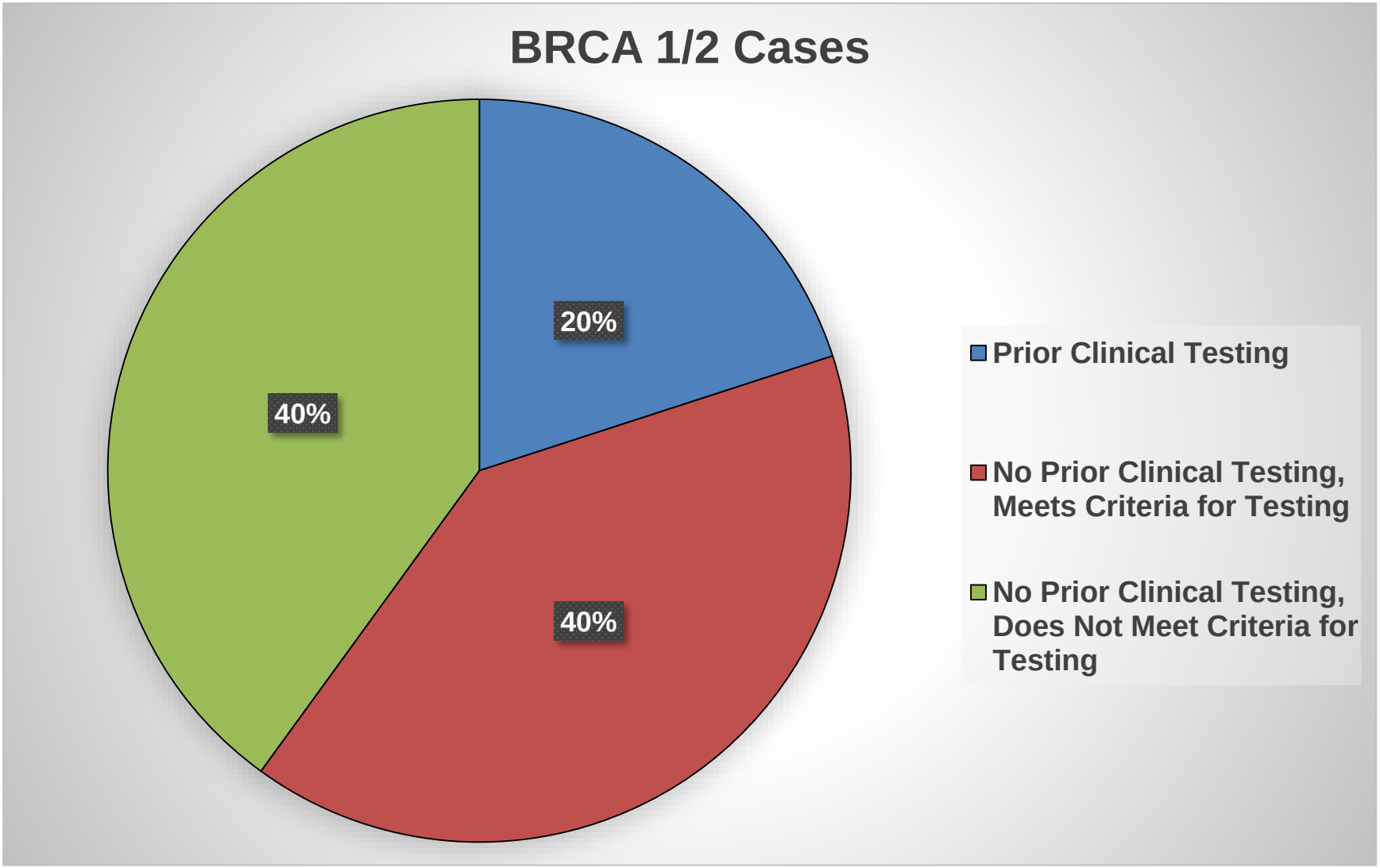


Genomic Screening Makes Invisible Risks Visible

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.”

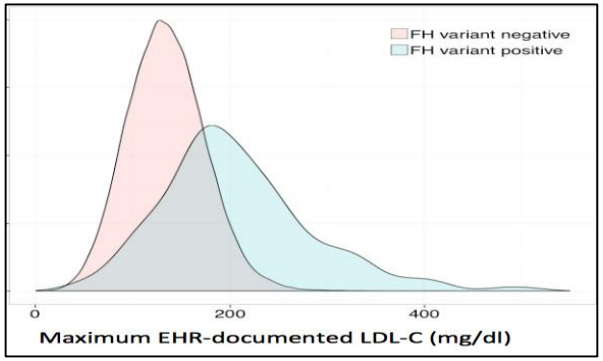
No personal or family history

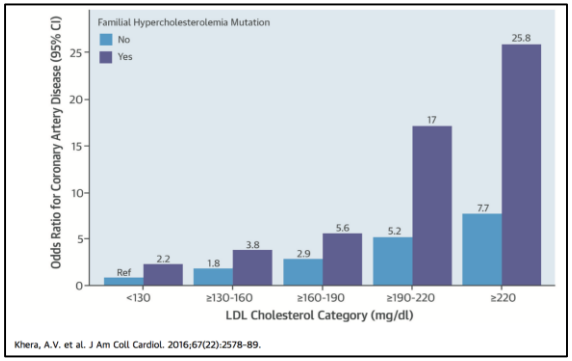
Genetic Follow-up

- 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

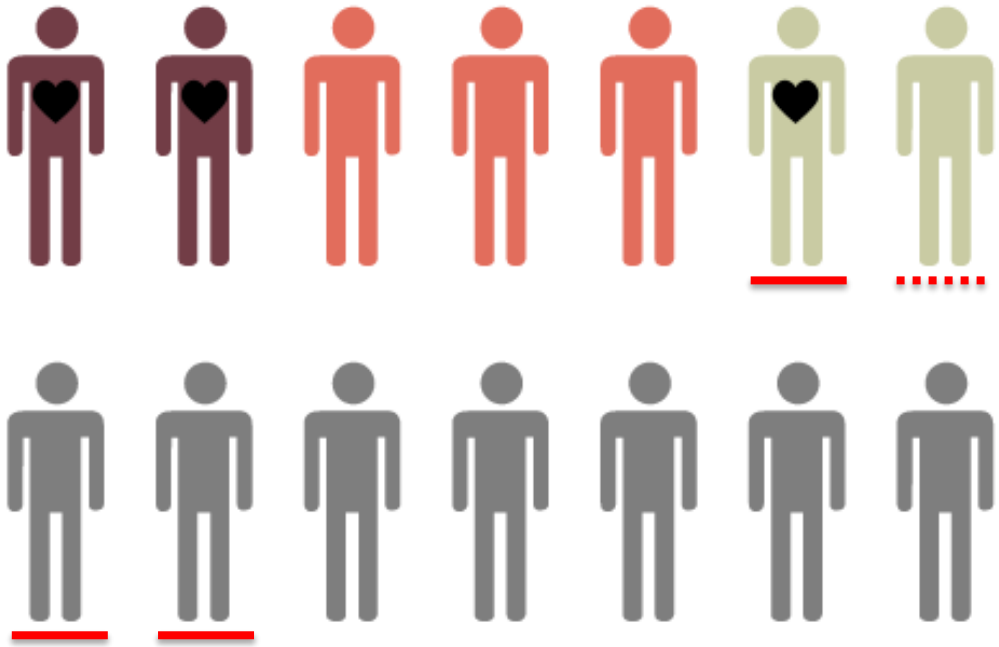
Familial Hypercholesterolemia





Correcting Misattribution Possible and it Matters

Cardiac Hypertrophy Prior to Results (N=14)

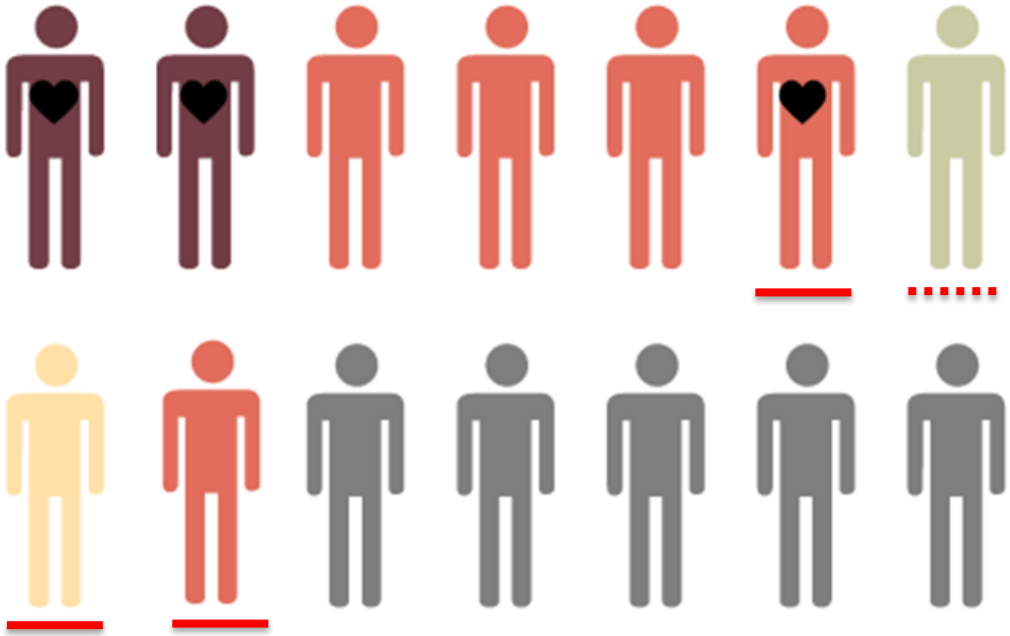


Mean age at diagnosis
46 y (range 27-62y)

- 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

Cascade Testing Extends the Reach

MyCode ROR Reach – Beyond Geisinger

ACKNOWLEDGEMENTS

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