Supplementary Materials

Supplementary Table 1: Definitions of personal and family history features and relevant disease risk management

Condition (Gene(s))	Personal history			Family history	
	Clinical diagnosis	**Relevant pre- and post-disclosure diagnoses**	**Relevant risk management**	**Clinical diagnosis**	**Suggestive history**
Familial hyper-cholesterol-emia (LDLR, APOB, PCSK9)	Familial hypercholesterol-emia	LDL-C ≥190mg/dL treated or untreated High cholesterol Hypercholesterolemia Dyslipidemia Coronary artery disease Medication list includes a lipid lowering therapy Myocardial infarction Peripheral vascular disease Claudication Atherosclerosis Cerebrovascular disease Xanthoma Xanthelasma Corneal Arcus	Appointments Cardiology appointment Pharmacy FH discussion Surveillance Lipid panel LDL Direct Lipoprotein(a) measurement Calcium Score Stress Echocardiogram Cardiac MRI Carotid Ultrasound Surgery Percutaneous coronary intervention Coronary artery bypass graft Carotid endartarectomy Medication initiation/change Initiate lipid-lowering therapy (if not on in last year) Increase dose of lipid-lowering therapy Add additional drug to ipid-lowering therapy Switch lipid-lowering therapy within class	Familial hypercholesterolemia	1 FDR or 2 SDRs with: High cholesterol and/or Coronary artery disease
Hereditary breast and ovarian cancer syndrome (BRCA1, BRCA2)	Hereditary breast and ovarian cancer syndrome	Breast cancer Ovarian cancer Pancreatic cancer Melanoma Prostate cancer	Appointments Inherited risk breast cancer clinic Surveillance Mammography Breast MRI CA-125 testing Transvaginal ultrasound Prostate-specific antigen Prophylactic surgery Risk-reducing mastectomy Risk-reducing salpingo-oophorectomy Chemoprevention tamoxifen raloxifene	Hereditary breast and ovarian cancer syndrome	1 FDR or 2 SDRs with: Breast cancer, Ovarian cancer, Pancreatic cancer, Melanoma, and/or Prostate cancer
Lynch syndrome (MLH1, MSH2, MSH6, PMS2)	Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer)	Colorectal cancer Endometrial cancer Gastric cancer Ovarian cancer Small bowel cancer	Appointments Inherited risk gastrointestinal clinic Surveillance Colonoscopy Upper endoscopy	Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer)	1 FDR or 2 SDRs with: Colorectal cancer, Endometrial cancer, Gastric cancer, Ovarian cancer,

		Hepatobiliary tract cancer Urinary tract cancer Brain cancer Sebaceous neoplasm Gastrointestinal adenoma	<u>Prophylactic surgery</u> Prophylactic hysterectomy Risk-reducing salpingo-oophorectomy		Small bowel cancer, Hepatobiliary tract cancer, Urinary tract cancer, Brain cancer, Sebaceous neoplasm, and/or Gastrointestinal adenoma

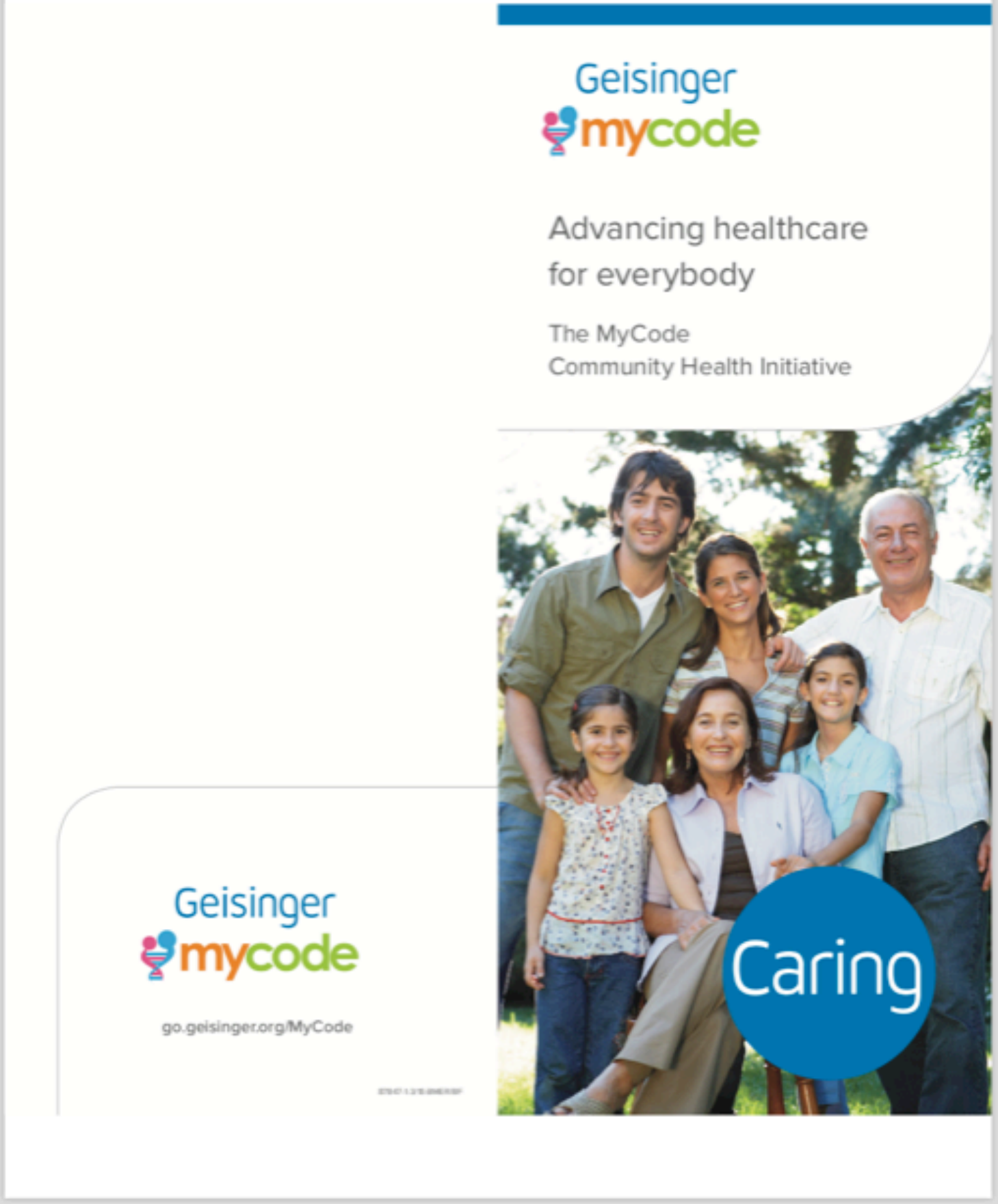
FDR=first-degree relative; SDR=second-degree relative, MRI=magnetic resonance imaging

Supplementary Table 2: Type and stage of post-disclosure cancer or precancerous lesion diagnoses

Condition	Gene	Cancer/Lesion Type	Stage/Notes
HBOC	*BRCA1*	Fallopian tube cancer	IC
HBOC	*BRCA1*	STIC lesion	N/A
HBOC	*BRCA2*	Breast cancer	DCIS
HBOC	*BRCA2*	Breast cancer	DCIS
HBOC	*BRCA2*	Breast cancer	IC
HBOC	*BRCA2*	Bilateral breast cancer	DCIS (bilateral)
HBOC	*BRCA2*	Ampulla of Vater cancer	IIB
HBOC	*BRCA2*	Prostate cancer	cT1c
HBOC	*BRCA2*	Prostate cancer	cT1c
HBOC	*BRCA2*	Prostate cancer	IIA
Lynch	*MSH2*	sebaceous adenomas (2)	Absent expression of MSH2/MSH6 proteins on immunohistochemistry in both adenomas
Lynch	*MSH2*	tubular adenoma (1)	no high-grade dysplasia
Lynch	*MSH6*	tubulovillous adenoma (1)	no high-grade dysplasia
Lynch	*PMS2*	tubular adenomas (2)	no high-grade dysplasia
Lynch	*PMS2*	tubular adenomas (2)	no high-grade dysplasia

HBOC=hereditary breast and ovarian cancer syndrome; STIC=serous tubal intraepithelial carcinoma; DCIS=ductal carcinoma in situ

Supplementary Figure 1: MyCode Community Health Initiative recruitment brochure



Be a part of something big

Geisinger is nationally recognized for its innovative approaches to improving the health of populations. MyCode is no exception. The MyCode® Community Health Initiative began in 2007 with the crucial support of the Geisinger patient community. This project holds the promise of new discoveries and treatments for serious chronic medical conditions that can affect our children, families, friends and communities.

If you decide to participate, you'll be joining hundreds of thousands of your friends and neighbors in an effort that may lead to better health for generations to come.

MyCode is a research study. Like all research studies that involve human subjects, there are some minor risks. We are happy to talk with you about the benefits and risks of joining.

Questions? Contact us.

Email: JoinMyCode@geisinger.org

Visit go.geisinger.org/MyCode or call toll free **855-636-0019** to find out more about participating.

What is MyCode?

MyCode is a Geisinger Precision Health project seeking new ways to improve the prevention, diagnosis, and management of disease.

Who is eligible?

All patients of Geisinger or Geisinger-affiliated hospitals and practices are invited to participate.

Will I learn anything?

Most people will not directly benefit from participating. However, up to 5 percent of MyCode participants will be contacted and told they have genetic changes that may indicate a higher risk for certain diseases and cancers. And even if you don't learn anything about your specific genes, all MyCode participants are contributing to our project goals of understanding the connection between genes and health.

Will Geisinger protect my privacy?

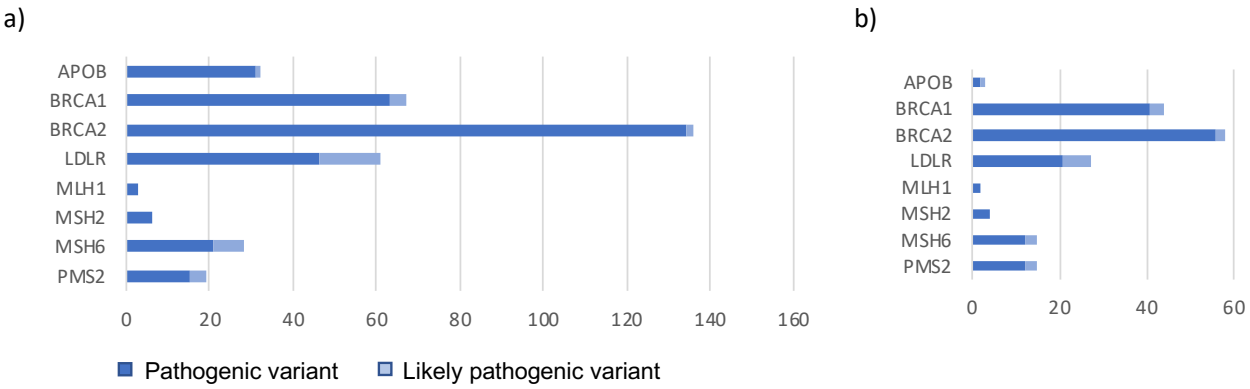
All MyCode data and samples are protected and confidential, according to Geisinger's strict privacy standards and HIPAA regulations. Your sample may be shared with Geisinger researchers and with Geisinger partners. No information that can identify you will be shared, and these researchers will not contact you directly.

What if I am concerned about my family history and genetics?

Ask your regular healthcare provider about Geisinger's genetic counseling services. He or she will discuss with you how to get appropriate screening and treatment if you have any concerns about family history or genetic illnesses.

Participating is easy. Talk to your healthcare provider today!

Supplementary Figure 2: Number of pathogenic and likely pathogenic (P/LP) variants identified per gene



a) study participants with a P/LP variant per gene; b) unique P/LP variants per gene in study participants

Supplementary Figure 3: Poster presentation at American College of Genetics & Genomics Annual Meeting

Impact of a Population Genomic Screening & Counseling Program on Risk Management Performance & Disease Diagnosis

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Background

- Population screening for genomic variants in CDC Tier 1 conditions can identify individuals at risk for preventable conditions who otherwise might not come to clinical attention prior to disease manifestation
- It is unclear whether genomic information found via screening guides care and reduces disease risk
- We reviewed EHR data for patients who received Tier 1 results via a genomic screening program in Geisinger's MyCode Community Health Initiative

Conclusions

A genomic screening program effectively identified previously undetected individuals at risk for hereditary cancer and heart disease

- Nearly 90% of individuals with a Tier 1 variant detected via genomic screening were previously unaware of their variant
- Yet, most of these had relevant personal and/or family history
- Two-thirds of patients subsequently performed disease risk management
- Rates of relevant history and post-disclosure risk management differed by Tier 1 condition
- More than 10% were diagnosed with pre-cancerous lesion, early-stage cancer, or atherosclerotic disease ***after*** disclosure of genomic result
- Post-disclosure genetic counseling was significantly associated with performing recommended risk management

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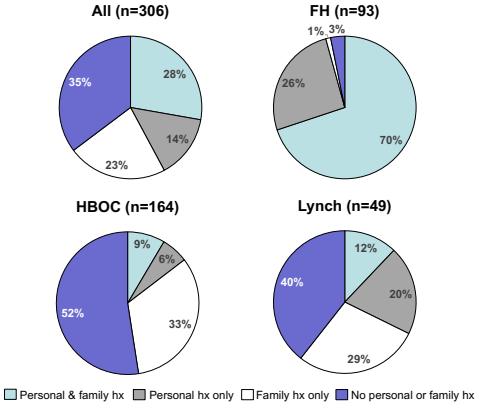
Methods

- MyCode participants' exome data reviewed for Tier 1 gene variants expected to be pathogenic (P) or likely pathogenic (LP)
- Variants confirmed in CLIA-certified laboratory, uploaded to electronic health record (EHR), & disclosed to patient-participants & their providers
- Study team reviewed EHR for percentage who:
  - were **not previously aware** of gene variant;
  - performed recommended **disease risk management post-disclosure** of genomic result (among those eligible by age, sex & previous treatment); &
  - had a **new diagnosis of relevant disease** post-disclosure

Results

- 1,061 of 64,394 MyCode participants (1.6%) received clinical report of P/LP variant in an actionable gene from May 2015-March 2019
- 512 of these (0.8%) had a Tier 1 gene result
- Chart reviews completed on 352 patients who received a Tier 1 result prior to February 2018
- 54% female, 99% European ancestry, 99% non-Hispanic ethnicity, median age of 63 years
- Median of 21.8 months from results disclosure to EHR review
- 13% of patients (n=46) already aware of their genomic result via clinical genetic testing prior to MyCode disclosure

Relevant personal & family history in EHR among patients without prior genetic diagnosis



Results

Risk management performance & post-disclosure diagnoses among eligible patients without prior genetic diagnosis

	FH (n=93)	HBOC (n=164)	Lynch (n=49)	All (n=306)
Risk Management Eligible[1]	93/93 (100%)	121/164 (73.8%)	49/49 (100%)	263/306 (86.0%)
Risk Management Pre-Disclosure[2]	69/93 (74.2%)	34/121 (28.1%)	30/49 (61.2%)	133/263 (50.6%)
Risk Management Post-Disclosure[3]	78/93 (83.9%)	75/121 (62.0%)	27/49 (55.1%)	180/263 (68.4%)
New Diagnosis[4]	26/93 (28.0%)	10/164 (6.1%)	5/49 (10.2%)	41/306 (13.4%)

[1]Eligible by age, sex & previous treatment to perform recommended risk management; [2]Performed risk management within recommended interval *prior* to disclosure; [3]Performed risk management *after* disclosure; [4]New diagnosis of relevant disease *after* disclosure

Post-disclosure diagnoses by condition (# patients)

FH (n=26)	HBOC (n=10)*	Lynch (n=5)
LDL-C >190 mg/dL (20)	Breast cancer (4)	Colon adenoma (4)
Atherosclerosis (5)	Prostate cancer (3)	Sebaceous adenoma (1)
Claudication/peripheral vascular disease (4)	Fallopian tube cancer (1)	
Corneal arcus (4)	STIC lesion (1)	
Xanthoma/ xanthelasma (3)	Ampulla of Vater cancer (1)	
Cerebrovascular accident (2)		

*All tumors stage IIA or earlier; STIC=serous tubal intraepithelial carcinoma

Variables significantly associated with post-disclosure risk management performance (logistic regression)

	OR (95% CI), p-value
Genetic counseling post-disclosure	2.59 (1.39, 4.80), p=0.003
Tier 1 Condition	
HBOC	Ref
FH	0.86 (0.26, 2.86)
Lynch	0.27 (0.11, 0.64), p=0.007
Pre-disclosure risk management	4.27 (2.08, 8.74), p<0.001

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