Moving Genomics into Everyday Health Care

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University of Utah
Department of Pathology Grand Rounds
April 20, 2023

Geisinger

Conflicts of Interest

Nothing to disclose

Outline

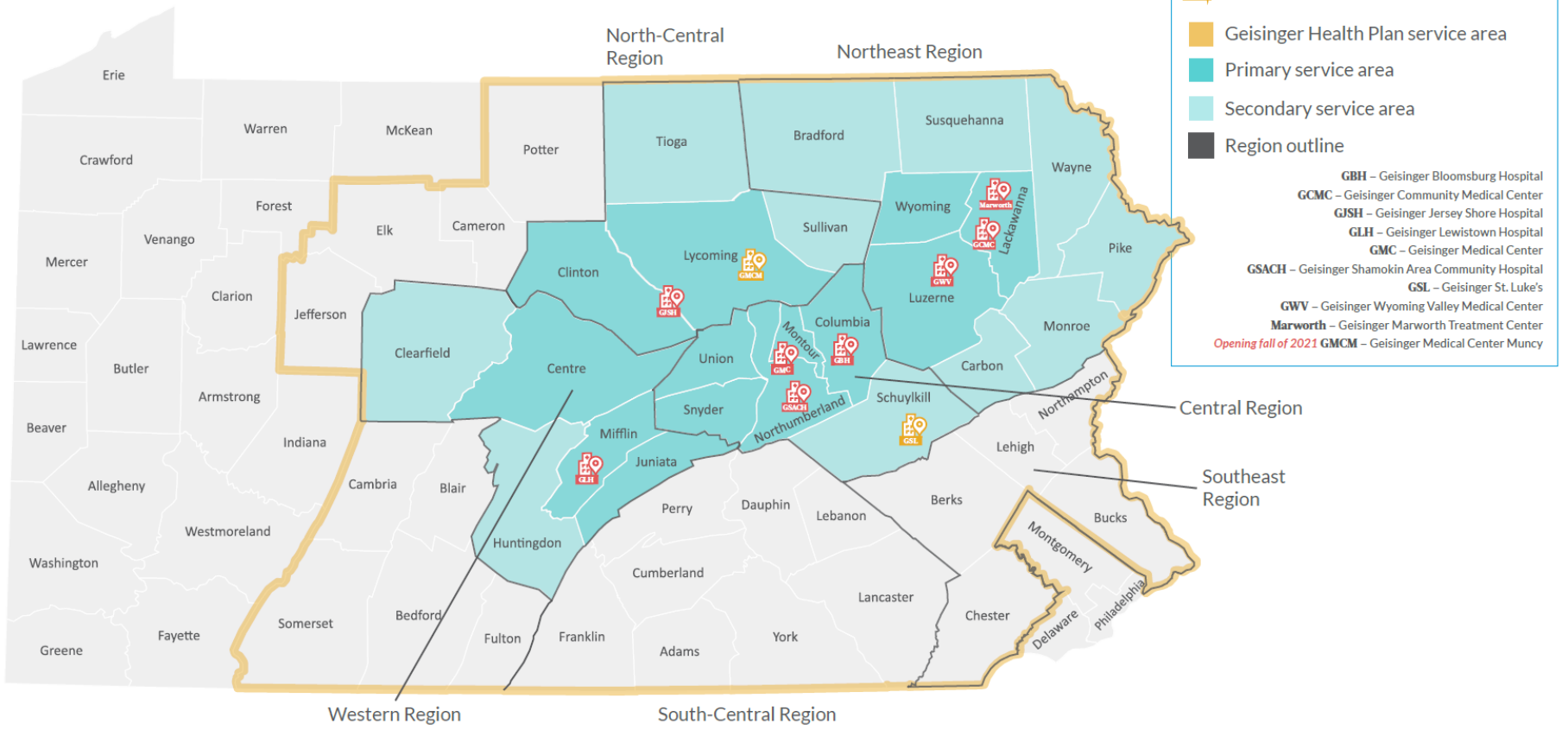
- Exploring Geisinger's MyCode Community Health Initiative
- Reporting Clinically Actionable Results to Patients
- Transitioning DNA Screening to the Clinic
- Expanding Precision Health to other Conditions

Life saving stories…

- ~40 year-old woman in MyCode research project found to have disease-causing change in the *KCNQ1* gene; her mother died suddenly in her sleep in her 20's
- *KCNQ1* – potassium channel gene; causes form of arrhythmia called Long QT syndrome which can result in sudden death
- Familial testing revealed her two sons also carry the change in *KCNQ1;* both have prolonged QT intervals, consistent with Long QT syndrome
- Mother and boys prescribed beta-blockers --- and family has automatic external defibrillator which they take to all of the boys' sporting events

"I thank God for this program, that this [mutation] was found and I'm not burying one of my kids."

Where is Geisinger?



- 10 hospital campuses
- 130 clinic sites
- ~3,000 providers; ~600 MBS/MD students; ~600 residents/fellows
- >1M active patients
- Geisinger Health Plan >550,000 members

mycode Community Health Initiative

- Population-based healthcare cohort recruited throughout the system using in-person (in clinics) and online (MyGeisinger) consenting
- High consent rate (~65-85%) – engaged community
- Exome and genotype data linked to clinical information from EHR (Epic since 1996) and claims data from Geisinger Health Plan
- Cohort Characteristics:
  - Most of European ancestry (~95%)
  - Median age of 54 years
  - Median 13.8 years of longitudinal EHR data

Carey et al. (2016) GIM

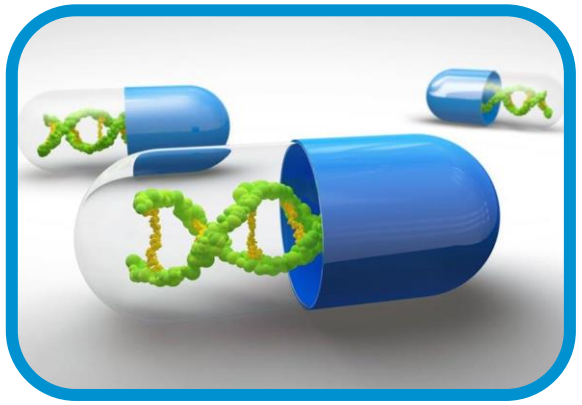
A study that spans the ages…

Loudon Tisinger
Enrolled at birth

Ruth Richards
Enrolled in her mid-90s; now over 100

MyCode has broad research goals

Discover gene-disease relationships



Target new drug development

MyCode variant confirmation.

POSITIVE

Result	Gene
PRESENT	BRCA2

Report results to individuals with actionable variants and conduct related research

Translate findings into clinical care

Google Scholar

As of 3/27/23

Geisinger MyCode

Geisinger MyCode Community Health Initiative
Verified email at geisinger.edu - Homepage

Precision Health

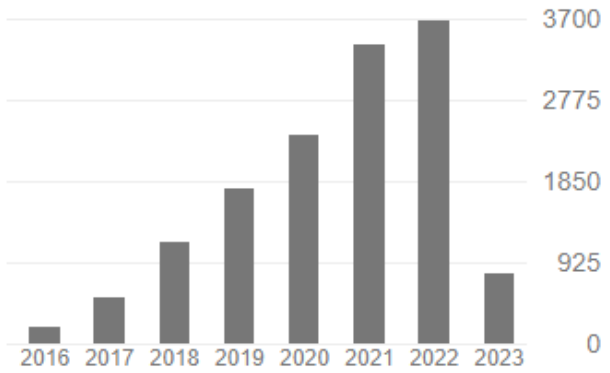
FOLLOW

GET MY OWN PROFILE

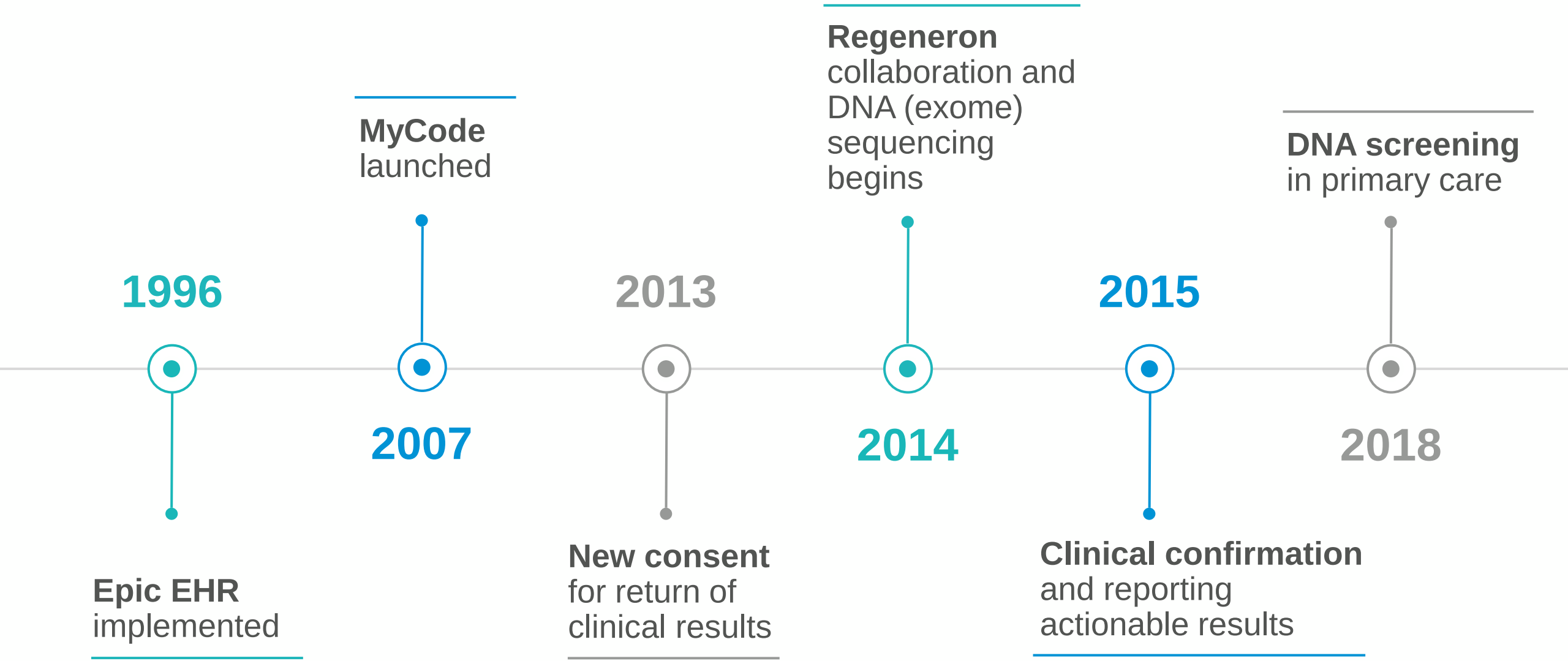
TITLE	CITED BY	YEAR
Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals JJ Lee, R Wedow, A Okbay, E Kong, O Maghzian, M Zacher, ... Nature genetics 50 (8), 1112-1121	1499	2018
Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease FE Dewey, V Gusarova, RL Dunbar, C O'Dushlaine, C Schurmann, ... New England Journal of Medicine 377 (3), 211-221	631	2017
Rare and low-frequency coding variants alter human adult height E Marouli, M Graff, C Medina-Gomez, KS Lo, AR Wood, TR Kjaer, RS Fine, ... Nature 542 (7640), 186-190	568	2017
A Protein-Truncating *HSD17B13* Variant and Protection from Chronic Liver Disease NS Abul-Husn, X Cheng, AH Li, Y Xin, C Schurmann, P Stevis, Y Liu, ... New England Journal of Medicine 378 (12), 1096-1106	527	2018

Cited by VIEW ALL

	All	Since 2018
Citations	14519	13316
h-index	57	53
i10-index	149	141



MyCode Timeline



DNA sequencing
will become a routine part of public health and medicine,
to improve individual **health and well-being**,
while maintaining or reducing the cost
of healthcare over the lifespan.

To do this, we need to **demonstrate the clinical utility and value** of genomic information at the **individual and population level**…

Geisinger is an ideal "healthcare laboratory"

- Dr. David Ledbetter, CSO Geisinger 2010-2021

What are the different types of studies that can be done on a person's DNA?

RECREATIONAL	CLINICALLY-INDICATED/ DIAGNOSTIC TESTING	POPULATION SCREENING
Discovery with limited results reporting	Indication specific *cancer, arrhythmia, autism, epilepsy…*	Targeted gene list for specific conditions (primarily *cancer, cardiac genes)*

23andMe

ancestry

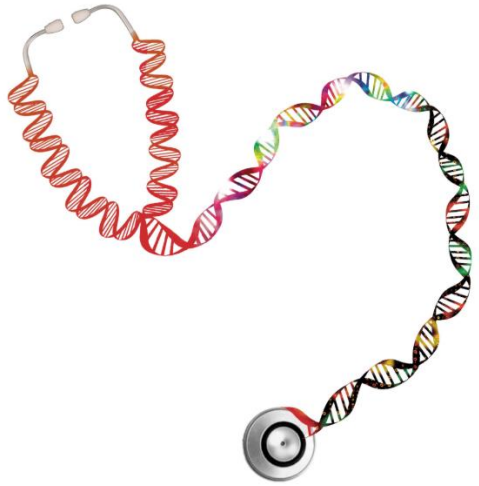


Image courtesy of the Human Genome Research Institute

mycode

MyCode® Scorecard

Total consented participants	327,789
Samples provided	227,981
DNA sequences available for research	184,293*
DNA sequences eligible and analyzed for clinical review	142,852*
Participants with clinical result reported	4,275

As of April 1, 2023

*These numbers are calculated from the current data set being evaluated and remain fixed for the duration of that data set. The remaining numbers are updated monthly.

Results disclosure for a clinically actionable set of genes (cancer, heart disease, etc.) – impacts about 1 in 30 (3%) individuals plus family members

Clinical Reporting Gene List

- **78 genes reviewed for *medical actionability* using:**
  - internal criteria
  - definitions proposed by the CDC (Tier 1)
  - definitions proposed by the ACMG secondary findings guidelines *(currently v3.1)*
- **Reportable results limited to:**
  - DNA changes that are known to cause disease (P/LP)
  - **We do NOT report variants of uncertain clinical significance!**
  - Specific disease-gene associations

Kelly et al. (2021) Am J Med Genet C Semin Med Genet.

MyCode Genomic Screening & Counseling (GSC)

Co-Directors:
Missie Kelly, MS, CGC
Jules Savatt, MS, CGC

Results Disclosure Process

MyCode Pipeline Identifies Variants Meeting Return Criteria

↓

Result is Clinically Confirmed

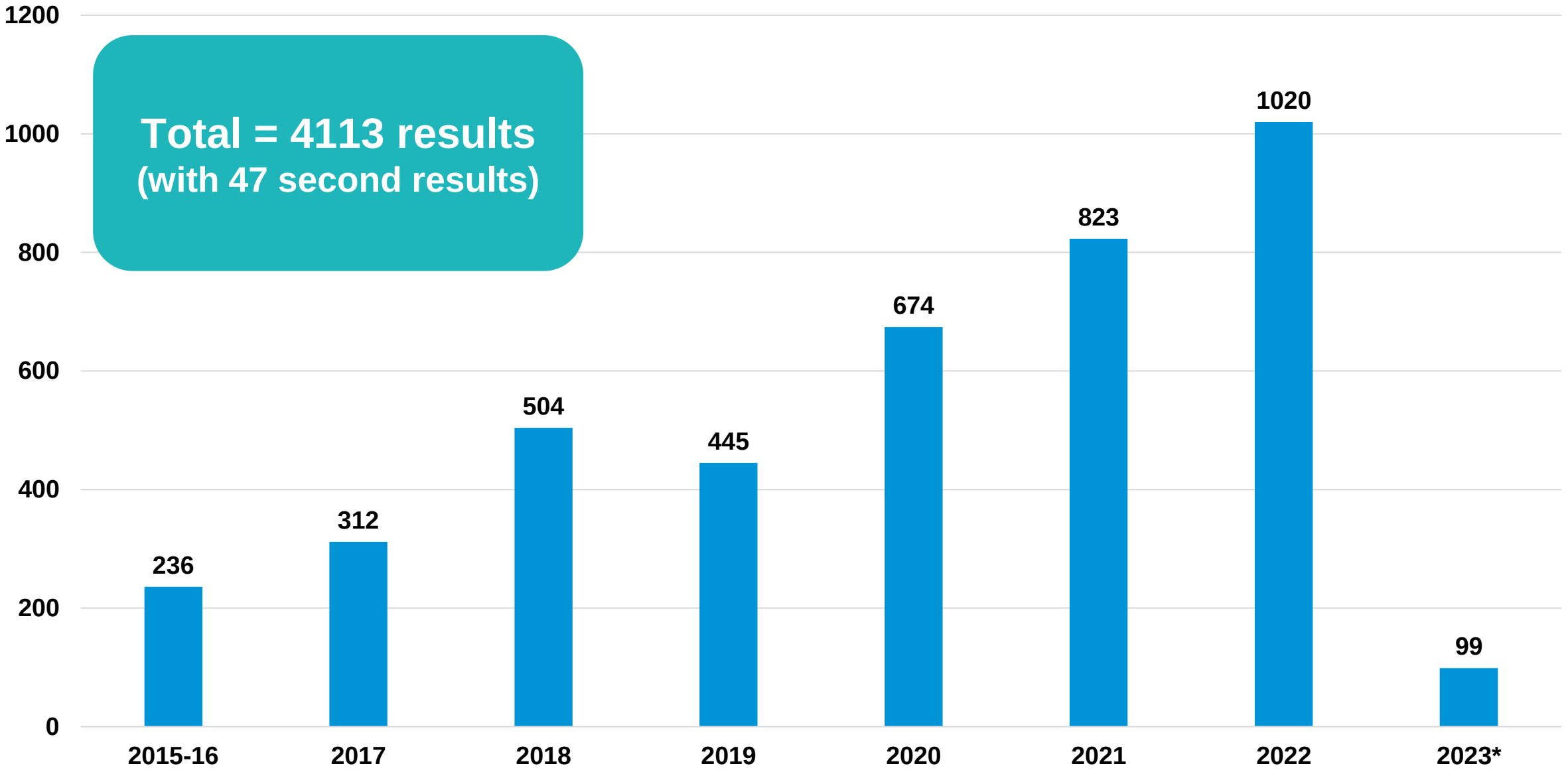
↓

Result is Uploaded to the EHR

↓

- Patient and their PCP are notified
- Patient is offered Genetic Counseling visit
- Patient and PCP are provided relevant resources

Annual MyCode Results Reported



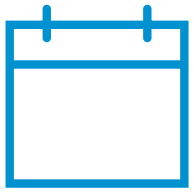
*As of 2/1/2023

2022 Results

1020 Results in 1013 Patients
(50 Unique Genes)

Patient and PCP Notification

- **84% (76%*) Successful Patient Disclosures**
- **16% (24%*) Patients Lost to Follow-up**

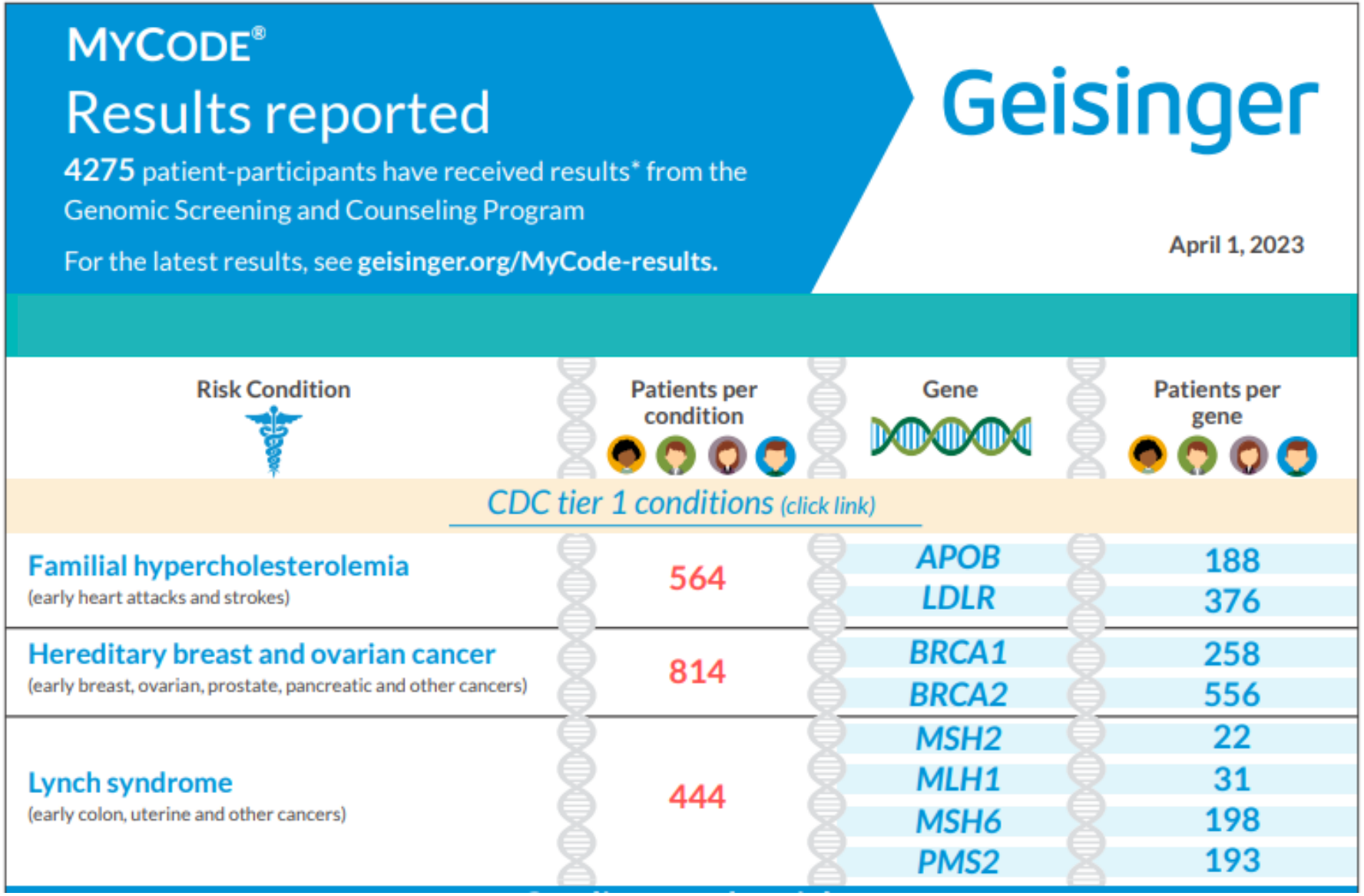


Patient Offered Genetic Counseling Visit

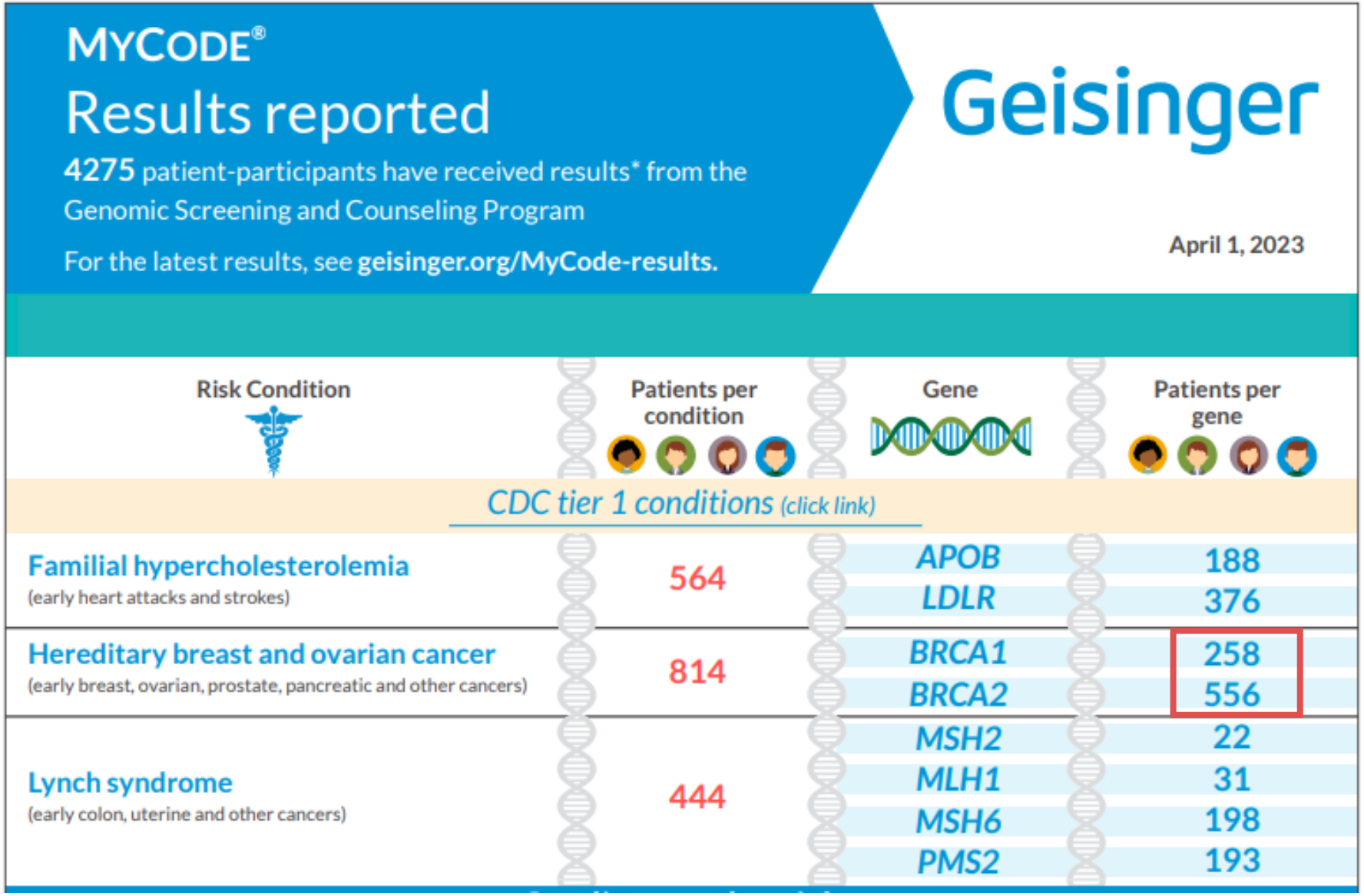
- **484 Completed Proband Visits**

* Initial Disclosure Attempt

43% of patient-participants received results in CDC Tier 1 genes



43% of patient-participants received results in CDC Tier 1 genes



MyCode®

Results reported

4275 patient-participants have received results* from the Genomic Screening and Counseling Program

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

Geisinger

April 1, 2023

Risk Condition	Patients per condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Familial hypercholesterolemia (early heart attacks and strokes)	564	*APOB*	188
		LDLR	376
Hereditary breast and ovarian cancer (early breast, ovarian, prostate, pancreatic and other cancers)	814	*BRCA1*	258
		BRCA2	556
Lynch syndrome (early colon, uterine and other cancers)	444	*MSH2*	22
		MLH1	31
		MSH6	198
		PMS2	193

As of April 1, 2023

Cardiovascular risk			
Hereditary transthyretin amyloidosis (buildup of amyloid in the body, can lead to heart and nervous system disease)	126	*TTR*	126
Heritable thoracic aortic disease (genetic predisposition to weakening of the wall of the aorta, leading to swelling and sometimes rupture)	39	*ACTA2*	39
Inherited arrhythmias (irregular heartbeat with risk for cardiac arrest)	350	*KCNE1*	3
		KCNH2	41
		KCNQ1	189
		SCN5A	117
Inherited cardiomyopathies (diseases of the heart muscle with dangerous complications)	831	*DSC2*	45
		DSG2	75
		DSP	72
		FLNC	16
		LMNA	21
		MYBPC3	173
		MYH7	75
		MYL2	8
		MYL3	7
		PRKAG2	1
		PKP2	79
		RBM20	1
		TNNI3	23
		TNNT2	10
		TPM1	5
		TTN	220

mycode

- Many DNA screening programs only test for the CDC Tier 1 conditions
- Our results show importance of including other genes

As of April 1, 2023

Cancer risk			
Familial adenomatous polyposis (intestinal polyps and early colon cancer)	48	*APC*	48
Hereditary pheochromocytomas and paragangliomas (tumors that can release extra hormones and, rarely, become cancer)	77	*SDHAF2*	7
		SDHB	38
		SDHC	19
		SDHD	9
		TMEM127	4
Li-Fraumeni syndrome (early breast, soft tissue, brain, adrenal and other cancers)	23	*TP53*	23
Multiple endocrine neoplasia type 1 (tumors that can release extra hormones and, rarely, become cancer)	14	*MEN1*	14
Multiple endocrine neoplasia type 2 (early thyroid cancer)	97	*RET*	97
***MUTYH*-associated polyposis** (intestinal polyps and early colon cancer)	3	*MUTYH*	3
Neurofibromatosis, type 2 (noncancerous tumors in nervous system)	1	*NF2*	1
***PALB2*-related cancer risk** (early onset breast, pancreatic, and ovarian cancers)	92	*PALB2*	92
Peutz-Jeghers syndrome (early breast, colon, pancreatic and other cancers)	2	*STK11*	2
Retinoblastoma (early eye cancer)	7	*RB1*	7

mycode

- Many DNA screening programs only test for the CDC Tier 1 conditions
- Our results show importance of including other genes

As of April 1, 2023

Miscellaneous phenotypes			
Biotinindase deficiency (buildup of a B vitamin in the body, can cause issues with the nervous system)	1	*BTD*	1
Fabry disease (enzyme defect leading to damage of blood vessels in the skin and cells in the kidneys, heart, and nervous system)	8	*GLA*	8
Hereditary hemochromatosis (too much iron in blood, can lead to liver and heart problems)	446	*HFE*	446
Hereditary hemorrhagic telangiectasia (abnormal blood vessel formation in skin, mucous membranes, lungs, liver and brain)	18	*ACVRL1* *ENG*	9 9
Juvenile polyposis (intestinal polyps, cancer of the intestine, including colon)	2	*BMPR1A*	2
Juvenile polyposis / hereditary hemorrhagic telangiecstasia (intestinal polyps, cancer of the intestine, including colon/ abnormal blood vessel formation in skin, mucous membranes, lungs, liver & brain)	2	*SMAD4*	2
Loeys-Dietz syndrome (weakening of the wall of the aorta, leading to swelling and sometimes rupture)	6	*SMAD3* *TGFBR1* *TGFBR2*	3 2 1
Malignant hyperthermia (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)	208	*RYR1*	208
Marfan syndrome (connective tissue disease that can cause heart, eye, and skeletal problems)	24	*FBN1*	24

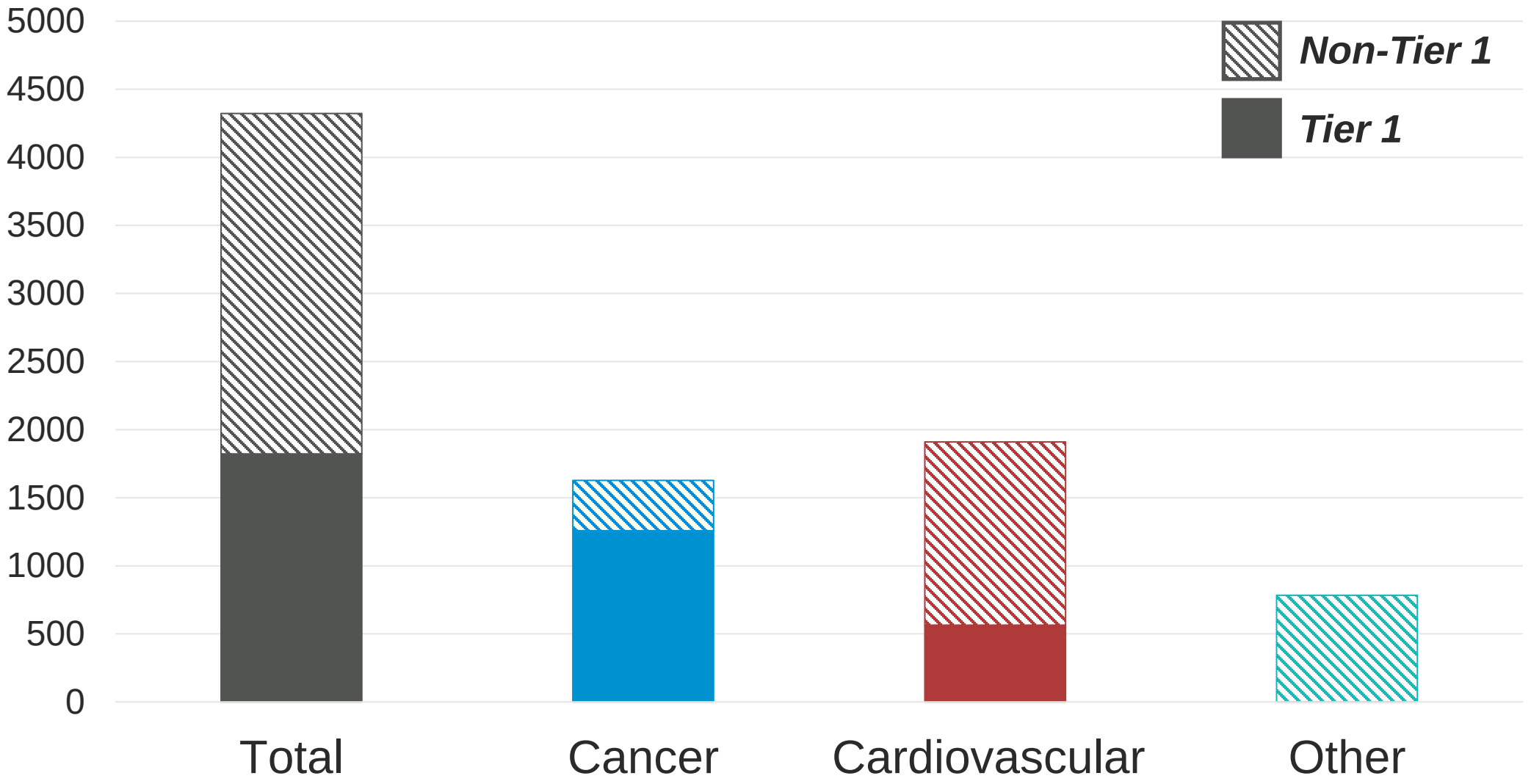
mycode

- Many DNA screening programs only test for the CDC Tier 1 conditions
- Our results show importance of including other genes

Results Reported

April 2023

Disease domains



Jeff's Story – *RET* gene

Multiple endocrine neoplasia type 2

- Male in 40s found to have disease-causing change in the *RET* gene
- No prior thyroid cancer or evaluation
- Met with genetics, PCP and ENT/surgical oncology
- Biopsy of nodule was benign, but elected for prophylactic thyroidectomy
- Post-surgery pathology found medullary thyroid microcarcinoma
- Resulted in cascade testing for multiple family members

Jeff's Story – *RET* gene

Multiple endocrine neoplasia type 2

"MyCode testing heavily influenced my treatment decision…I felt a prophylactic thyroidectomy was the way to go…MyCode gave my patient the information he needed to make an informed decision."

- Dr. Nicholas Purdy
Jeff's surgical oncologist

"If it wasn't for MyCode, I would not have had the operation, and they would not have found the cancer. Finding this so early on made the experience truly worthwhile."

- Jeff, MyCode Patient Participant

Jeff's Story – *RET* gene

Multiple endocrine neoplasia type 2

Dr. Nicholas Purdy

JAMA Otolaryngology-Head & Neck Surgery | Original Investigation

Published online January 5, 2023

Thyroidectomy Outcomes in Patients Identified With *RET* Pathogenic Variants Through a Population Genomic Screening Program

Priscilla F. A. Pichardo, DO; Ryan N. Hellums, DO; Jing Hao, MD, PhD; Juliann M. Savatt, MS; Dina Hassen, MPP; Phillip K. Pellitteri, DO; Madiha Alvi, MD; Adam H. Buchanan, MS, MPH; Nicholas C. Purdy, DO

MyCode results are impacting physician practice

- “The first time I had a patient with hemochromatosis found through MyCode I started looking for hemochromatosis routinely in my other patients.”

- “It’s a real asset to be able to refer patients with familial hypercholesterolemia to a lipid specialist who can get them to their cholesterol goal effectively.”

Dr. Suzy Kobylinski
Chair, Community Medicine

Significant clinical impact for patients & families

Participants with clinical result reported

>4,275

=100 people

Buchanan AH et al., 2020, *Genet Med;*
Manickam K et al., 2018, *JAMA Netw Open*

Significant clinical impact for patients & families

Participants with clinical result reported

>4,275

~90% learned of their risk through MyCode

=100 people

Buchanan AH et al., 2020, *Genet Med;* Manickam K et al., 2018, *JAMA Netw Open*

Significant clinical impact for patients & families

Participants with clinical result reported

>4,275

~90% learned of their risk through MyCode

Most patients don't meet clinical testing requirements (based on personal and family history)

=100 people

Buchanan AH et al., 2020, *Genet Med;* Manickam K et al., 2018, *JAMA Netw Open*

Significant clinical impact for patients & families

Participants with clinical result reported

>4,275

~90% learned of their risk through MyCode

~~50%~~ *of individuals with BRCA1/2 variants do not meet clinical testing guidelines*

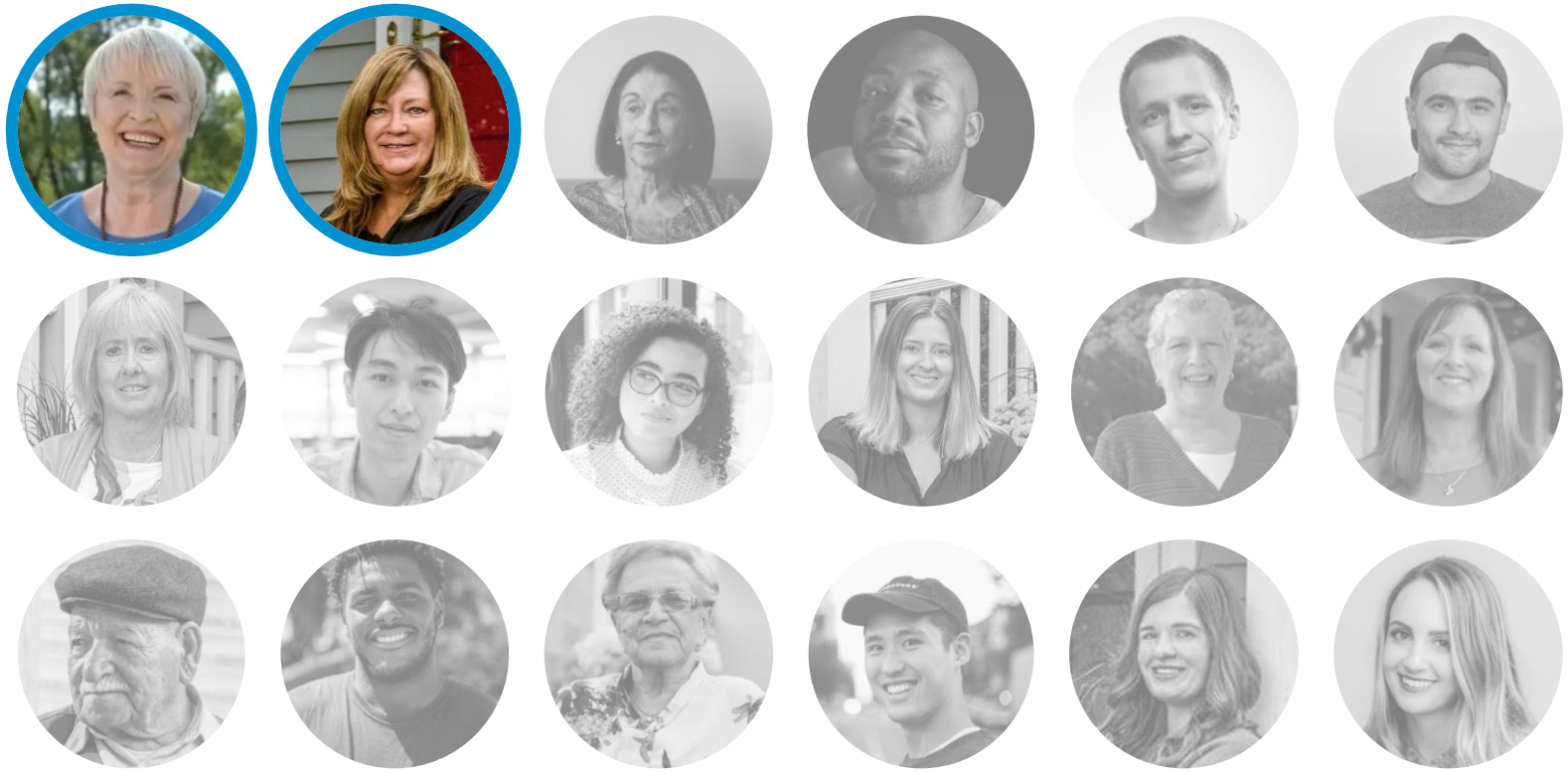
=100 people

Buchanan AH et al., 2020, *Genet Med;* Manickam K et al., 2018, *JAMA Netw Open*

Significant clinical impact for patients & families

Participants with clinical result reported

>4,275



~13% with post-disclosure diagnosis of heart disease or early-stage cancer (Tier 1 conditions)

=100 people

Private Information

Buchanan AH et al., 2020, *Genet Med;* Manickam K et al., 2018, *JAMA Netw Open*

Significant clinical impact for patients & families

Participants with clinical result reported	>4,275

8 at-risk close relatives per participant with clinical result

>34,000 at-risk relatives, half of whom carry the same genetic change

MyCode Genomic Screening & Counseling

More thorough ascertainment of risk

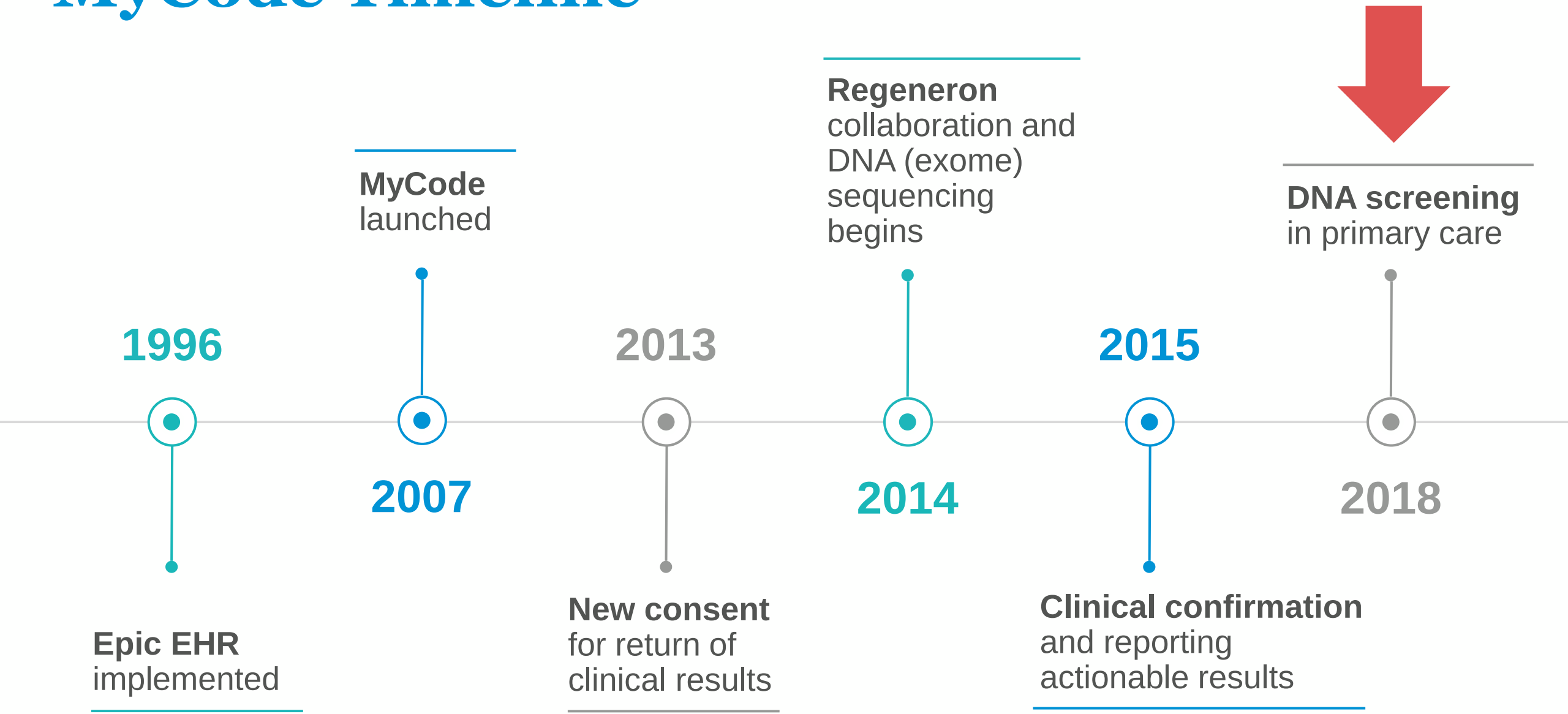
Disease prevention & early detection

Better outcomes for patients & families

Population Health DNA Screening:

Building programs
to incorporate precision health
into everyday health care
for ALL of our patients.

MyCode Timeline



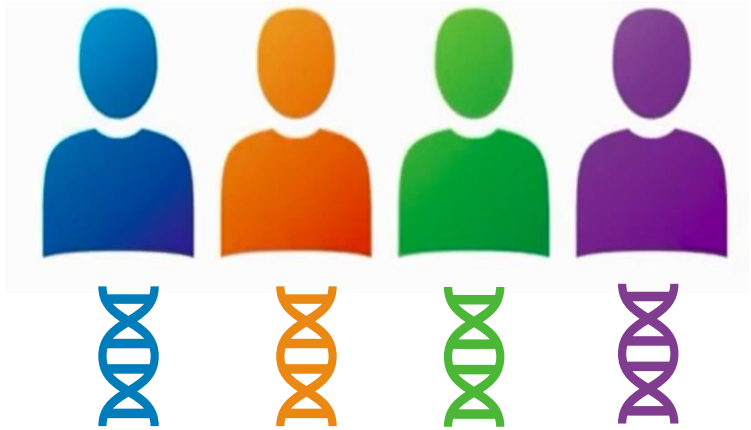
We can provide more targeted, preventive care now

2021

Population Screen				
DNA Test Result	✗	✓	✓	✓
	BRCA1			
Follow-up Consult	***Cancer clinic***			

We can provide more targeted, preventive care now

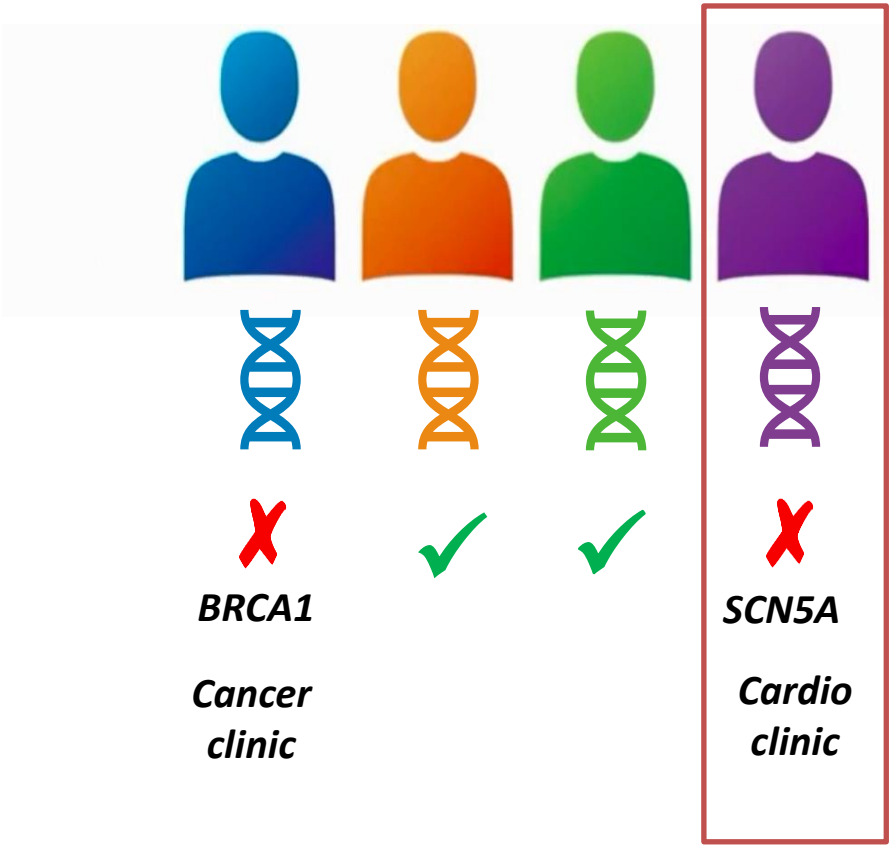
2021



Population Screen				
DNA Test Result	✗	✓	✓	✓
	BRCA1			
Follow-up Consult	*Cancer clinic*			

Over time, we can update results

2025



	✗	✓	✓	✗
	BRCA1			*SCN5A*
	Cancer clinic			*Cardio clinic*

Report updated on results from same sample based on new understanding or genes

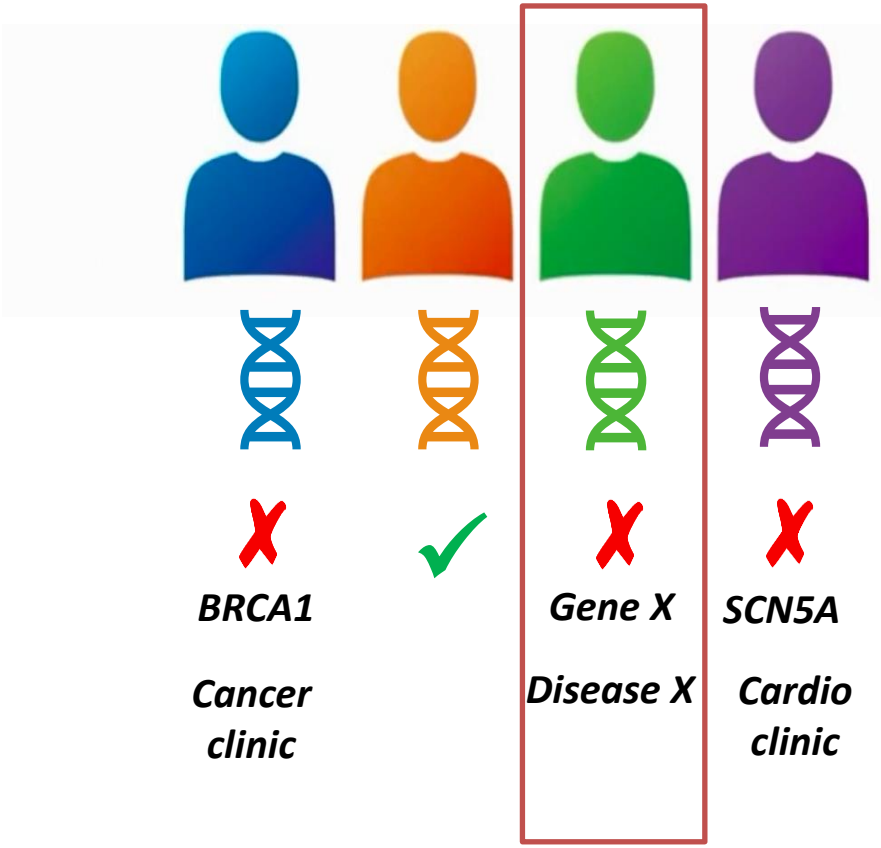
We can provide more targeted, preventive care now

2021

Population Screen				
DNA Test Result	✗	✓	✓	✓
	BRCA1			
Follow-up Consult	*Cancer clinic*			

Over time, we can update results

2030



	✗	✓	✗	✗
	BRCA1		*Gene X*	*SCN5A*
	Cancer clinic		*Disease X*	*Cardio clinic*

Report updated on results from same sample based on new understanding or genes

Population Health DNA Screening

A clinical transition from the MyCode Research Project

- Clinical pilot launched in July 2018 in single primary care clinic
- Now launched in ~20 primary care and specialty clinics
- *Anticipatory care for disease prevention* instead of reactionary treatment
- *Earlier detection* of disease to enable better management and improved outcomes
- *More reliable identification of risk for patients and their families* to develop diseases like:
  - Hereditary breast and ovarian cancer
  - Familial hypercholesterolemia
  - Lynch cancer syndrome
  - Cardiac arrhythmias

DNA test ordering and results incorporated into medical record – like any other clinical test

myGeisinger.org *A Convenient Way to Manage Your Health*

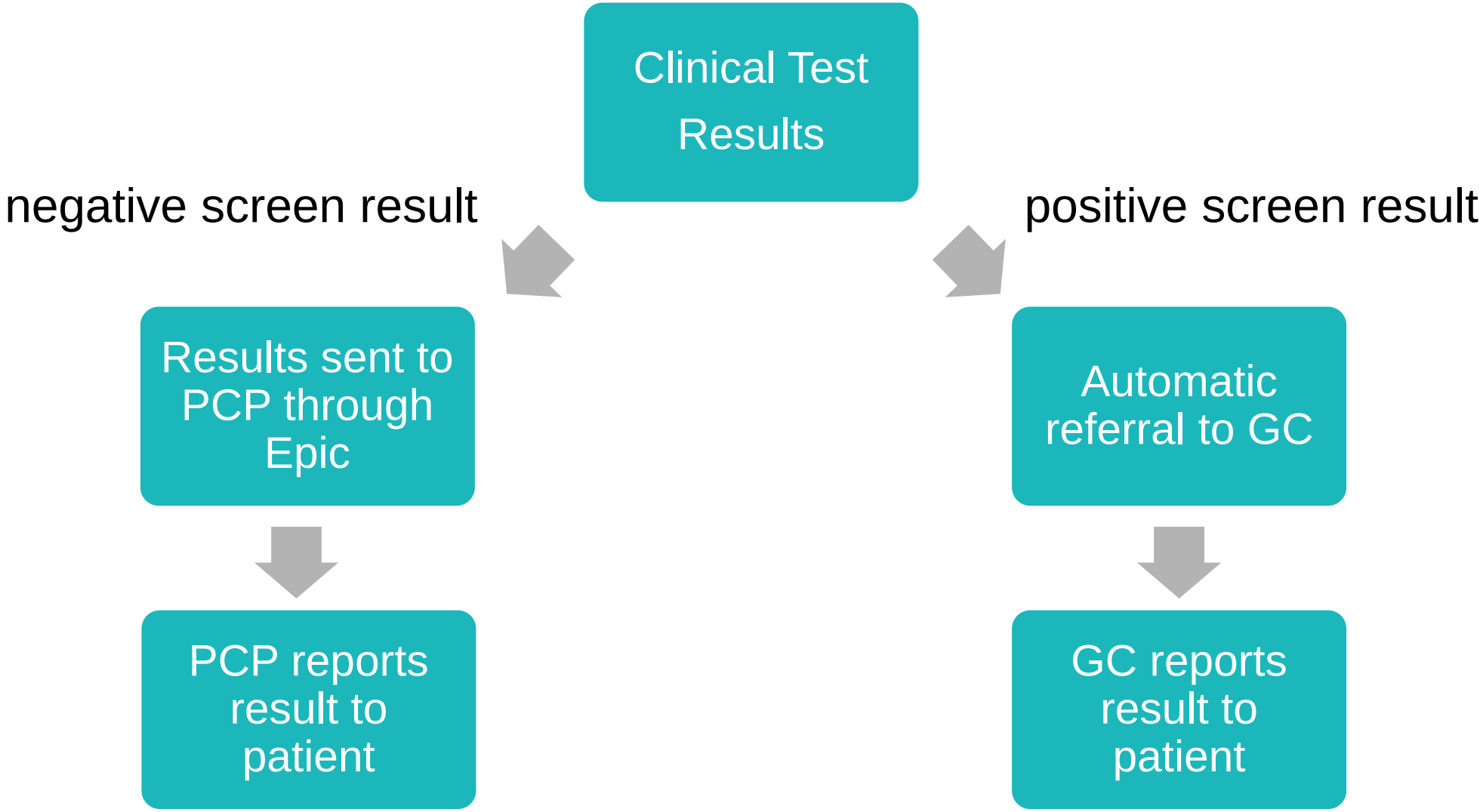
LIPID PANEL
Ordered by David D K Rolston, MD on July 13, 2018
Expected: Jul 13, 2018 (approximately)
Expires: Oct 13, 2018

BASIC METAB PANEL, BMP
Ordered by David D K Rolston, MD on July 13, 2018
Expected: Jul 13, 2018 (approximately)
Expires: Oct 13, 2018

WHOLE EXOME SEQUENCING-POPULATION HEALTH SUBSET
Ordered by David D K Rolston, MD on July 13, 2018
Expected: Jul 13, 2018 (approximately)
Expires: Oct 13, 2018

PSA
Ordered by David D K Rolston, MD on July 13, 2018
Expected: Jul 13, 2018 (approximately)
Expires: Oct 13, 2018

Result Reporting



Just-in-Time Physician Education

What you need to know.

When you need to know.

All in one page.

Pathogenic/Likely Pathogenic *BRCA1* Variant: Clinical Next Steps

Patient has increased risk for associated cancers – breast, ovarian, pancreatic, prostate

1. Evaluate patient for history and symptoms of associated cancers
2. Manage risk according to clinical evaluation and published guidelines summarized below[1]
3. Encourage patient to share result with at-risk relatives
    - First-degree relatives (parents, siblings, children) have 50% risk of inheriting familial *BRCA1* variant

Clinical resources at Geisinger

- Clinical Genomics (XX referral and contact info for on-call genetic counselor)
- Inherited Risk Breast Clinic (XX referral and contact info)

Cancer Risks[2,3,4]

Cancer Type	*BRCA1*-Associated Cancer Risk	General Population Risk
Female breast	46%-79%	12%
2nd primary breast	21% within 10 years	2% within 5 years
Ovarian	39%-53%	1%-2%
Pancreatic	1%-3%	0.5%
Male breast	1%-2%	0.1%
Prostate	Up to 33%	11%

Geisinger

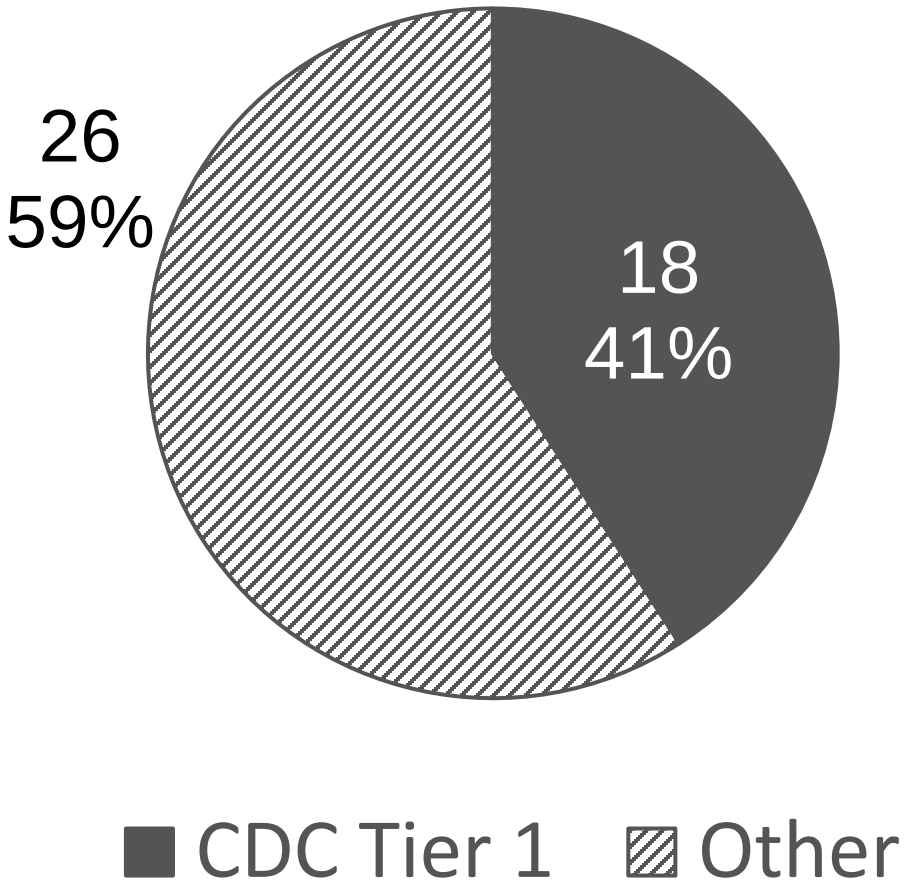
Population Health DNA Screening Positives

Positive Results

- Tests completed: 1335
- Positive Results: 44

  3.29% overall

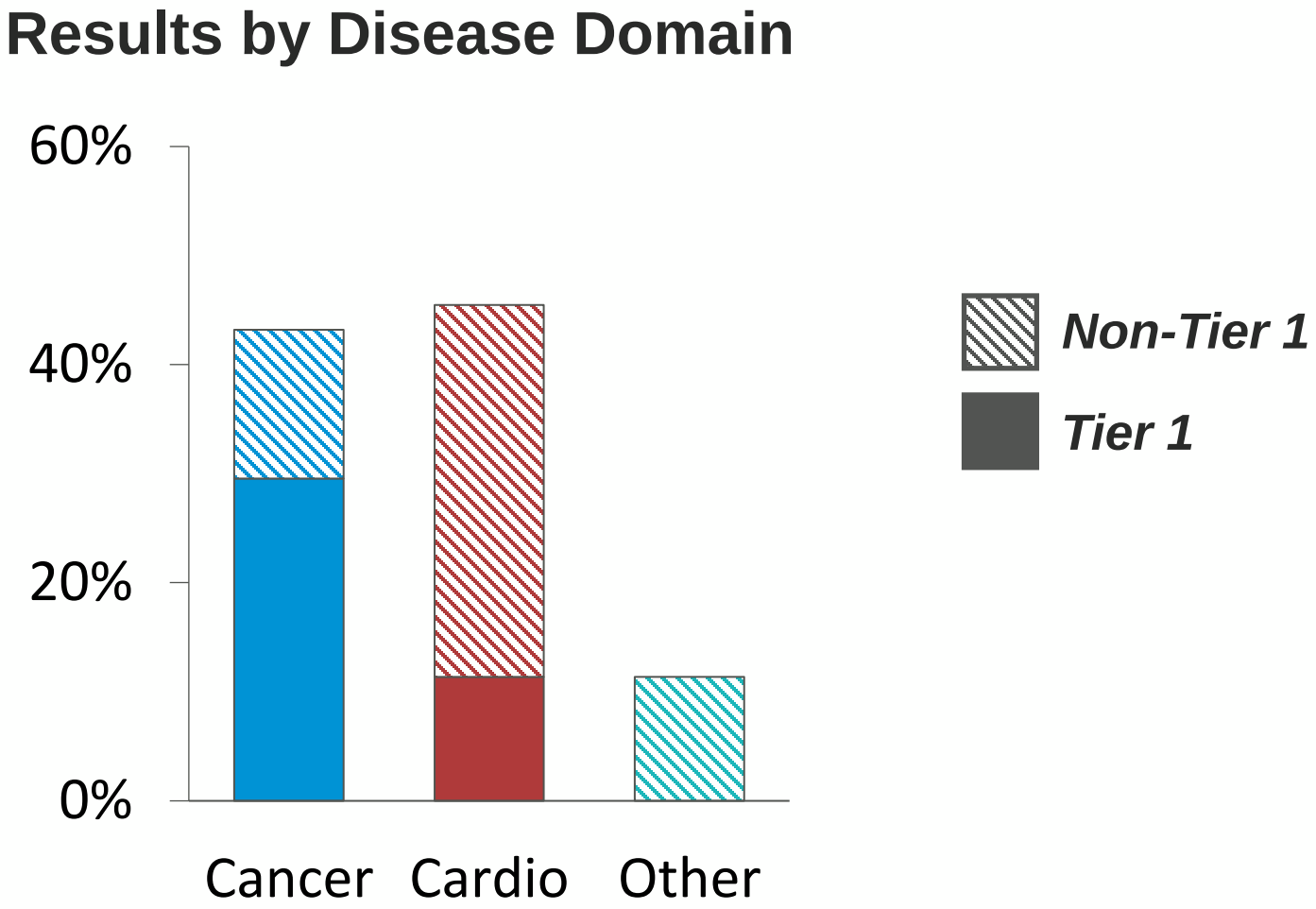
  1.35% CDC Tier 1



As of 3/20/23

Population Health DNA Screening Positives

Positive Results



Population Health DNA Screening

Summary

- Our data support routine genomic screening for CDC Tier 1 Applications – including HBOC, Lynch syndrome, and familial hypercholesterolemia – *as well as other genetic disorders*
- ~50% of patients with a positive genetic result don't meet routine criteria for genetic testing
- Growing evidence that receiving positive result leads to surveillance and earlier detection or prevention of disease
- Continue to evaluate feasibility of broader routine screening with decreasing sequencing costs – cost of test vs cost avoidance, etc.

What about Precision Health for other conditions?

Precision Health for Brain Disorders

Life Changing Stories

- 48-year old man found to have pathogenic 22q11.2 deletion
- Lives with parents, single, graduated HS, certificate in welding, drives, independently manages appointments / finances
- Typical 22q11.2 deletion facial appearance; no history of chronic medical conditions or surgeries
- Psychotic episode at 35, required hospitalization; psychiatry attempted discontinuation of medication at age 40 with recurrence of psychosis
- 22q del diagnosis supported continued treatment; currently stable on low dose of antipsychotic medication

"It feels good to know that there's a medical name for my condition."

Neurodevelopmental/Psychiatric Disorders (NPD)

- Characterized by impairments in cognition, communication, behavior, and/or motor functioning
- Impact about 14-18% of the nation's children and adults
- ~30% have genetic etiology, including copy number variants (CNVs) and single gene disorders
- Shared genetic etiologies among NPD :

- autism spectrum disorder
- intellectual disability/ developmental delay
- epilepsy
- ADHD
- cerebral palsy
- bipolar disorder
- schizophrenia
- depression
- anxiety

Unbiased, Genotype First Ascertainment of NPD

- To date, most studies on the neurodevelopmental/psychiatric phenotypic effects of genomic variants have investigated clinical or research cohorts ascertained for ID, ASD, SCZ, or other disorders.
- These largely pediatric studies are biased towards the most severe phenotypic consequences of genomic variants.
- More data is needed on the clinical consequences of genomic variants in unselected populations to understand broader phenotypes.
- Population-based studies are also needed to more accurately estimate the prevalence and penetrance of genomic causes of NPD and assess potential utility in broad health care.

MyCode Cohort

CNV and SNV Analysis for NPD

- 90,620 patient-participants with sequence data passing QC for exome-based CNV calling and single gene loss-of-function (LOF) variant analyses
- Determined frequency of genomic variants in:
  - **31 pathogenic recurrent NPD copy number regions** (>250kb; e.g., 22q11.2 deletion; ClinGen Dosage Score = 3)
  - **94 high-confidence NPD genes** (P/LP LOF variants)
- Examined penetrance of NPD in individuals with CNV and single gene variants

NPD genomic variants in MyCode

Prevalence, penetrance, and personal utility

JAMA Psychiatry | Original Investigation

2020: 77(12):1276-1285

Identification of Neuropsychiatric Copy Number Variants in a Health Care System Population

Christa Lese Martin, PhD; Karen E. Wain, MS; Matthew T. Oetjens, PhD; Kasia Tolwinski, PhD; Emily Palen, MS; Abby Hare-Harris, PhD; Lukas Habegger, PhD, MS; Evan K. Maxwell, PhD, MS; Jeffrey G. Reid, PhD; Lauren Kasparson Walsh, MS; Scott M. Myers, MD; David H. Ledbetter, PhD

Am J Psychiatry 180:1, January 2023

Prevalence and Penetrance of Rare Pathogenic Variants in Neurodevelopmental Psychiatric Genes in a Health Care System Population

Hermela Shimelis, Ph.D., Matthew T. Oetjens, Ph.D., Lauren K. Walsh, M.S., Karen E. Wain, M.S., Masa Znidarsic, M.D., Scott M. Myers, M.D., Brenda M. Finucane, M.S., David H. Ledbetter, Ph.D., Christa Lese Martin, Ph.D.

MyCode Cohort CNV Analysis - Prevalence

- 708/90,595 **(0.8%)** individuals have a pathogenic CNV
  - Most common deletion – 16p13.11
  - Most common duplication – 22q11.2
- *Only* 41/708 **(5.8%)** had a previously known genetic diagnosis in the EHR
  - Mean age = 20.33 yrs (compared to 50.04 yrs for all CNV+ individuals)
  - Younger patients more likely to have genetic testing

MyCode Cohort CNV Analysis - Penetrance

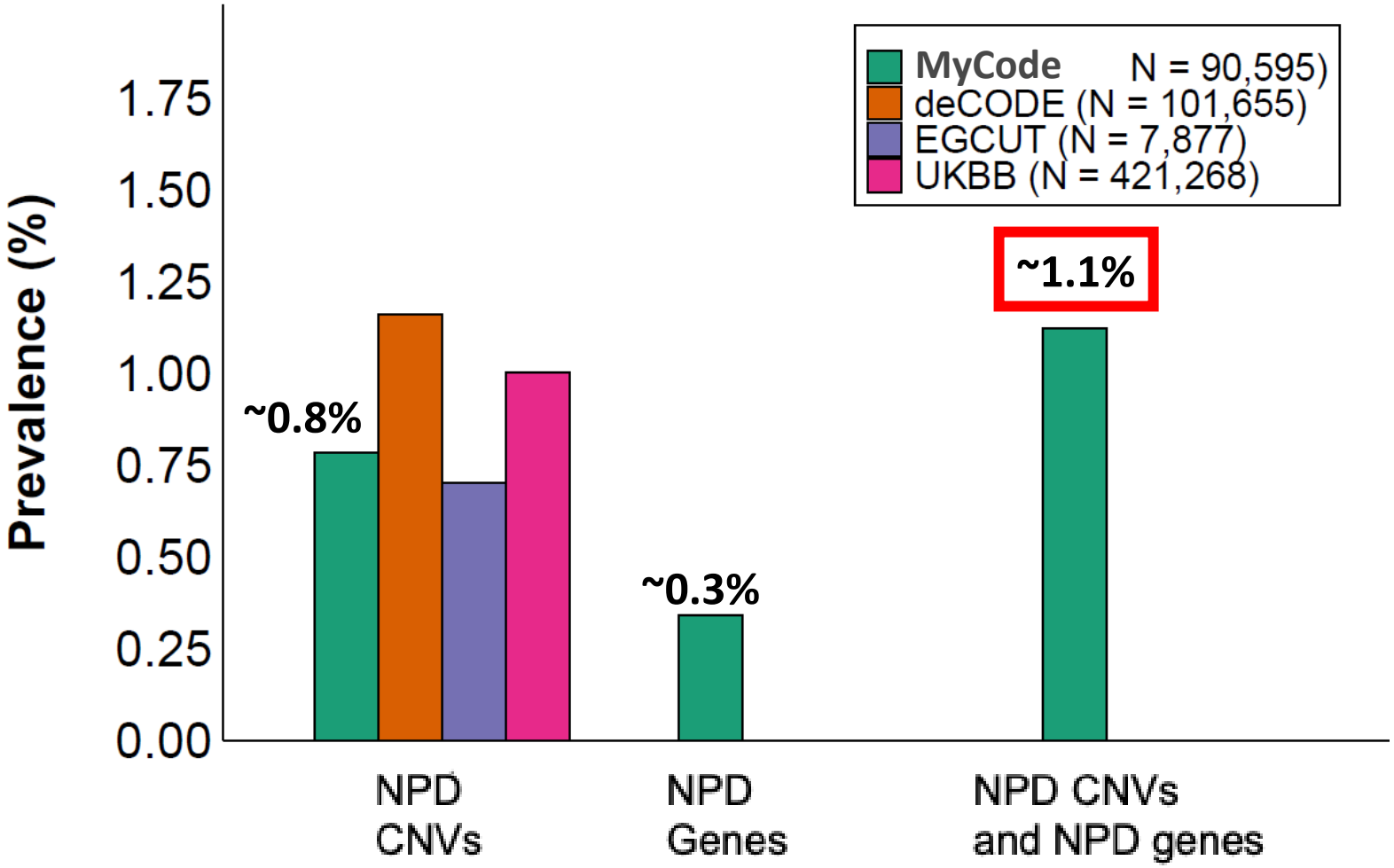
70% (494/708) of participants had ≥1 clinical symptom consistent with CNV diagnosis

(including NPD and other congenital malformations)

Prevalence – NPD gene LOF variants

- Pathogenic variants identified in **0.34%** (312/90,595) of individuals in 61 of 94 genes
- The genes with the highest frequency of variants are:
  - *ANK2* with 26 (0.029%)
  - *ASXL3* with 21 (0.023%)
  - *SHANK2* with 18 (0.020%)

Prevalence of Pathogenic Variants in 31 NPD Recurrent CNVs and 94 NPD Genes in MyCode and Other Population-based cohorts



Shimelis and Oetjens et al. (2023) Am J Psychiatry

Penetrance – NPD gene LOF variants

- Overall, **71.2%** (222/312) of variant-positive individuals had NPD, including depression and anxiety, and/or a congenital anomaly
- **34.3%** (107/312) of variant-positive individuals had a diagnosis of NPD compared to 14.6% (13,105/89,577) of those without a variant ($p<0.0001$).
- **68.6%** (214/312) of variant-positive individuals had a diagnosis of NPD (broadened to depression and anxiety) compared to 57.4% (13,105/89,577) of those without a variant ($p=8.11 \times 10^{-5}$).
- **10.9%** (34/312) of variant-positive individuals had a congenital anomaly codes (central nervous system, cardiac, renal/urinary, genital, cleft lip/palate) compared to 7.9% (7,067/89,577) of those without a variant ($p=0.06$).

Disclosing NPD CNVs to MyCode Participants

Personal Utility

Select CNVs to be disclosed:

- Include recurrent, pathogenic CNVs mediated by segmental duplications
- Clinical phenotypes that include NPD
- Prioritized CNVs based on number and type of non-NPD medical implications

Requirements for returning results:

- Originally required participant to have NPD/CM documented in EHR; but now expanded to anyone with CNV regardless of EHR data
- Age 18 years or older
- Adequate consents on file and adequate sample available for clinical confirmation

9 CNVs
1q21.1 deletion
7q11.23 deletion
15q13.3 deletion
15q24 deletion
16p11.2 deletion
16p13.11 deletion
17q11.2 (NF1) deletion
17q12 deletion
22q11.2 deletion

Major Themes from CNV Disclosure Sessions Were Consistent Across Data-Sets

Discussed NPD history (e.g., learning/ interpersonal difficulties) and lifelong challenges that were not recorded in EHR	"I was a slow learner." (Female, 17q11.2) "I was left out… I was different from other kids." (Female, 1q21.1)
Had previously explained NPD as a result of social circumstances (trauma, personal issues, family disruption)	"I do put a lot of [my learning disability on] what happened between mom and dad and the moving around." (Male, 16p11.2)
Expressed that CNV "fit" or "made sense" with lived experience	"I knew I had anxiety. I knew I had different things, but I didn't know where everything came from. This now brings everything around." (Female, 1q21.1)
Felt reassured that NPD was not their fault	"It was very helpful. It took a lot of guilt off." (Mother of Male, 22q11.2)
Reported that "sense of self" stayed the same or improved	"I think it does [change sense of self], because I realize there's a medical, that's something behind everything. It's not just all in your head." (Female, 1q21.1)
Positive and negative emotions were often expressed together	"I thought it was something bad, but it's bad and a good thing at the same time, that information that you gave me." (Female, 17q11.2)
Believed information to be valuable, for themselves and family members	"It feels good to know that there's a name for my condition." (Male, 22q11.2) "If this information is something that we can help [our son]… it's good to know that now and not more when he's… We can get a little bit more control of it now." (Wife of Male, 16p13.11)

Mixed Methods Assessment of Participant Experience

- Participants described CNV results as **personally valuable**.
- **Positive responses outweighed negative** responses. Negative emotions were related to recounting past experiences.
- **Results are actively incorporated** into personal narratives, their “sense of self” and their understanding of their medical and family histories.
- Participants were **open to discussing their NPD history** with the GC and often **planned to share CNV result with family and healthcare providers**.

NPD Precision Health: Key Take-Aways

- **Recurrent pathogenic NPD CNVs were observed in 0.8% of participants**
  - The majority of adults **(5.8%)** with NPD CNVs have not received a genetic diagnosis

- **NPD gene variants were identified in 0.34% of participants**

- **Taken together, rare NPD variants are prevalent (1.1%), representing 1 in 89 MyCode participants,** and play an important contributory role in mental health disorders
  - This prevalence is lower-bound, minimum estimate, since we limited our analyses to a conservative list of 31 pathogenic, recurrent CNVs and pathogenic/likely pathogenic LOF variants in 94 high-confidence NPD genes

NPD Precision Health: Key Take-Aways

- **NPD pathogenic variants (CNVs and SNVs) result in clinical symptoms (penetrance) at similar rates to other genomic disorders included in population health screening (35-70%)**

- **Participants value receiving NPD CNV results and describe the experience as important and valuable**
  - Clinically and psychologically important – **"medicalizing" NPD**
  - May decrease stigma, increase self-advocacy, and lead to closer engagement with healthcare providers

- **Population screening for NPD pathogenic variants to identify high-risk groups could improve clinical outcomes through early intervention and anticipatory therapeutic support.**

Genetics in Medicine

Volume 24, Issue 3, March 2022, Pages 703-711

Article

Medical manifestations and health care utilization among adult MyCode participants with neurodevelopmental psychiatric copy number variants

Brenda Finucane [1], Matthew T. Oetjens [1], Alicia Johns [2], Scott M. Myers [1], Ciaran Fisher [1], Lukas Habegger [3], Evan K. Maxwell [3], Jeffrey G. Reid [3], David H. Ledbetter [1], H. Lester Kirchner [2], Christa Lese Martin [1]

- Increased risk of chronic diseases including diabetes (2X) and dementia (2X)
- Increased ED visits (2X)

Realizing the Potential of Genomics across the Continuum of Precision Health Care

Prevention

Screening for monogenic and/or polygenic risk

Carrier screening

PGx

Early Detection

Multi-cancer early detection blood testing

Genotype-first medicine

Clinical Diagnosis

Exomes/Genomes

Prenatal
NICU
Neurodevelopment
Medical Genetics
Cardiology
Cancer

Treatment

PGx

Targeted therapies

Clinical trials

Surveillance

Minimal residual disease blood testing

Dynamic ongoing genomic analysis

Opportunistic Family Exomes/Genomes and Cascade Testing

Genomic Data Warehouse

Ongoing Analysis

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Thank You.