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Supplemental information

Prospective, multi-site study of healthcare utilization after actionable monogenic findings from clinical sequencing

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Supplemental Materials and Methods

Supplemental Methods:

Chart review methods

During the study, process and clinical outcomes were abstracted after manual review of individuals' electronic health records. Manual review was limited to participants who received P/LP results and was conducted at six and 12 months post return. Abstracted test types were based on standard clinical guidelines for care after the return of results (RoR) of P/LP findings. The network entered de-identified outcome data into REDCap projects housed at the coordinating center. To ensure consistency across the network, abstraction guides were developed by condition leads to assist coordinators in pulling and entering data. Training and review of questions were discussed on workgroup calls and abstraction guides were updated accordingly to assist with uniform data collection across all 10 sites.

High-throughput assessment

The HI-TAG knowledge base contains 321 unique CPT codes that were categorized into 73 code clusters (services) each representing a single type of test or procedure (# clusters/condition): arrhythmia (18); BCa (18), cardiomyopathy (26), CRC (8), FH (3). The knowledge base was generated by gathering lists of commonly utilized CPT codes for the five conditions from site physician condition experts and online look up tools such as the American Medical Association and American Academy of Professional Codes. CPT code sets were manually grouped into categories based on similarity, and frequency counts were generated to verify utilization within at least one center. The analyses presented in this paper include all process outcome related CPT codes listed in HI-TAG unless otherwise noted.

Validation of HI-TAG

HI-TAG services were compared to manual chart review conducted during the study. In some cases, multiple HI-TAG services were linked to one chart review variable as the CPT data were more granular than the study assessments. CPT data were truncated to 12-month post return and compared to results from chart review. To avoid underpowered comparisons, validation of HI-TAG was conducted only on test types that exceeded 10 observations.

For events where there was disagreement between the HI-TAG method and the chart review, a secondary chart review at three centers (Vanderbilt University Medical Center, Columbia, and Northwestern) was conducted to adjudicate conflicting results. Analysis was conducted on a per participant basis and positive predictive value (PPV) and sensitivity are reported along with 95%

confidence intervals for each group of CPTs based on the adjudicated reference standard (**Figure S1**). Average sensitivity ranged from 0.55 to 0.84 [Arrhythmia (0.75); BCa (0.76), Cardiomyopathy (0.84), CRC (0.55), FH (0.71)] and PPV ranged from 0.64 to 0.90 [Arrhythmia (0.87); BCa (0.81), Cardiomyopathy (0.90), CRC (0.90), FH (0.64)].

Table S1. HI-TAG database. See accompanying excel document. First tab displays a summary of services examined for each condition including counts of CPT code types included in a given service and how many codes were considered primarily evaluation screening. Subsequent tabs list the codes and descriptions for each condition and service.

Condition	Guideline	Recommended surveillance testing	Adult age range
Arrhythmia	AHA 2023[1]	Electrocardiogram, rhythm surveillance (various)	40+
Cardiomyopathy	AHA & ACC 2020[2]	Echocardiography (primary), Cardiac MRI	40+
Familial Hypercholesterolemia	Various[3]	Lipid profile, Lipoprotein (a) one time	18+
Hereditary Breast and Ovarian Cancer (BCa)	NCCN 2021[4]	Mammogram (with tomosynthesis), Breast MRI	25-75
Lynch Syndrome (CRC)	NCCN 2021[5]	Colonoscopy every 1-2 years at age 25	25-75

Table S2. Post return guideline-based testing and age ranges. BCa: Breast Cancer, CRC: Colorectal Cancer.

Arrhythmia		**Breast cancer**		**Cardiomyopathy**		**Colorectal cancer**		**FH**	
Gene	OMIM	Gene	OMIM	Gene	OMIM	Gene	OMIM	Gene	OMIM
CACNA1A	601011	*ATM*	607585	*ACTC1*	613424	*APC*	611731	*APOB*	107730
KCNE1	613695	*BRCA1*	604370	*DSC2*	125645	*BMPR1A*	174900	*APOE*	617347
KCNE2	613693	*BRCA2*	114480	*DSG2*	612877	*JAK2*	147796	*LDLR*	605747
KCNH2	613688	*CHEK2*	114480	*DSP*	605676	*MLH1*	609310	*PCSK9*	607786
KCNQ1	607542	*JAK2*	147796	*GLA*	301500	*MSH2*	120435		
LMNA	150330	*PALB2*	620442	*HFE*	613609	*MSH6*	614350		
RYR2	115000	*PTEN*	601728	*LMNA*	115200	*MUTYH*	604933		
SCN5A	603830	*TP53*	191170	*MYBPC3*	615396	*POLE*	615083		
				MYH7	613426	*PTEN*	158350		
				MYL2	608758	*SMAD4*	174900		
				MYL3	608751	*STK11*	175200		
				PKP2	602861	*PMS2*	600259		
				PRKAG2	600858				
				TMEM43	612048				
				TNNI3	613286				
				TNNT2	601494				
				TPM1	611878				

Table S3. Gene and OMIM numbers associated with conditions examined. Individuals with P/LP findings in the below genes were grouped by condition for analysis. FH: Familial Hypercholesterolemia.

	Arrhythmia		BCa		Cardiomyopathy		CRC		FH	
Total	95		96		95		105		86	
Female	55		96		58		66		54	
Male	40		0		37		39		32	
Age										
<40	11		12		21		25		17	
40-75	68		56		62		61		56	
>75	16		12		12		19		13	
Race & Ethnicity	**P/LP**	**Neg**	**P/LP**	**Neg**	**P/LP**	**Neg**	**P/LP**	**Neg**	**P/LP**	**Neg**
White	93	84	86	86	84	81	101	94	81	78
Black	2	11	6	7	7	12	2	6	4	6
Asian	0	0	1	0	2	1	0	1	0	2
Other/unknown	0	0	3	3	2	1	2	4	1	0
Hispanic	0	2	5	3	4	2	3	7	1	2
Non-Hispanic	94	93	89	90	91	92	100	95	85	84
Unknown	1	0	2	3	0	1	2	3	0	0

Table S4. Participants with Pathogenic or Likely Pathogenic (P/LP) findings and those with no P/LP variants (Neg: negative reports) stratified by demographics. BCa: breast cancer; CRC: colorectal cancer; FH: familial hypercholesterolemia.

Condition	P/LP Pre-RoR	P/LP Post-RoR	Neg Pre-RoR	Neg Post-RoR	Difference in difference
Arrhythmia	0 (0, 1)	1 (0, 3)	0 (0, 2)	0 (0, 1)	1 (0, 3.5)
Breast Cancer	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 1)
Cardiomyopathy	0 (0, 2)	2 (0, 4)	0 (0, 0)	0 (0, 2)	1 (-2, 3)
Colorectal cancer	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)
Familial hypercholesterolemia	0 (0, 1)	0 (0, 1.8)	0 (0, 1)	0 (0, 1)	0 (-1, 1)

Table S5. Frequency of health care tests or procedures over one year. Results are presented stratified by condition comparing test counts over one year period prior to return of results (Pre-RoR) and after return of results (Post-RoR) among the individuals receiving pathogenic/likely pathogenic (P/LP) and those receiving negative (Neg) reports. A difference in difference analysis compares the change in P/LP associated healthcare utilization over time to the change associated with negative report return. Values are median rates with interquartile range.

Condition	P/LP Pre-RoR	P/LP Post-RoR	Neg Pre-RoR	Neg Post-RoR	Difference in difference
Arrhythmia	0 (0, 25.9)	136.7 (0, 456.0)	0 (0, 156.2)	0 (0, 25.9)	0 (0, 456.0)
Breast Cancer	0 (0, 0)	0 (0, 186.1)	0 (0, 0)	0 (0, 0)	0 (0, 149.0)
Cardiomyopathy	0 (0, 303.8)	304.4 (0, 740.1)	0 (0, 0)	0 (0, 151.6)	182.7 (0, 691.4)
Colorectal cancer	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 4.1)
Familial hypercholesterolemia	0 (0, 11.6)	0 (0, 18.7)	0 (0, 11.6)	0 (0, 11.6)	0 (0, 11.3)

Table S6. Cost differences between participants receiving P/LP and negative reports. Results are presented stratified by condition comparing costs prior to return of results (Pre-RoR) and after return of results (Post-RoR) among the individuals receiving pathogenic/likely pathogenic (P/LP) and those receiving negative (Neg) reports. A difference in difference analysis compares the change in P/LP report rates over time to the change in negative report rates over time. Values are median rates per year with interquartile range and given in dollars.

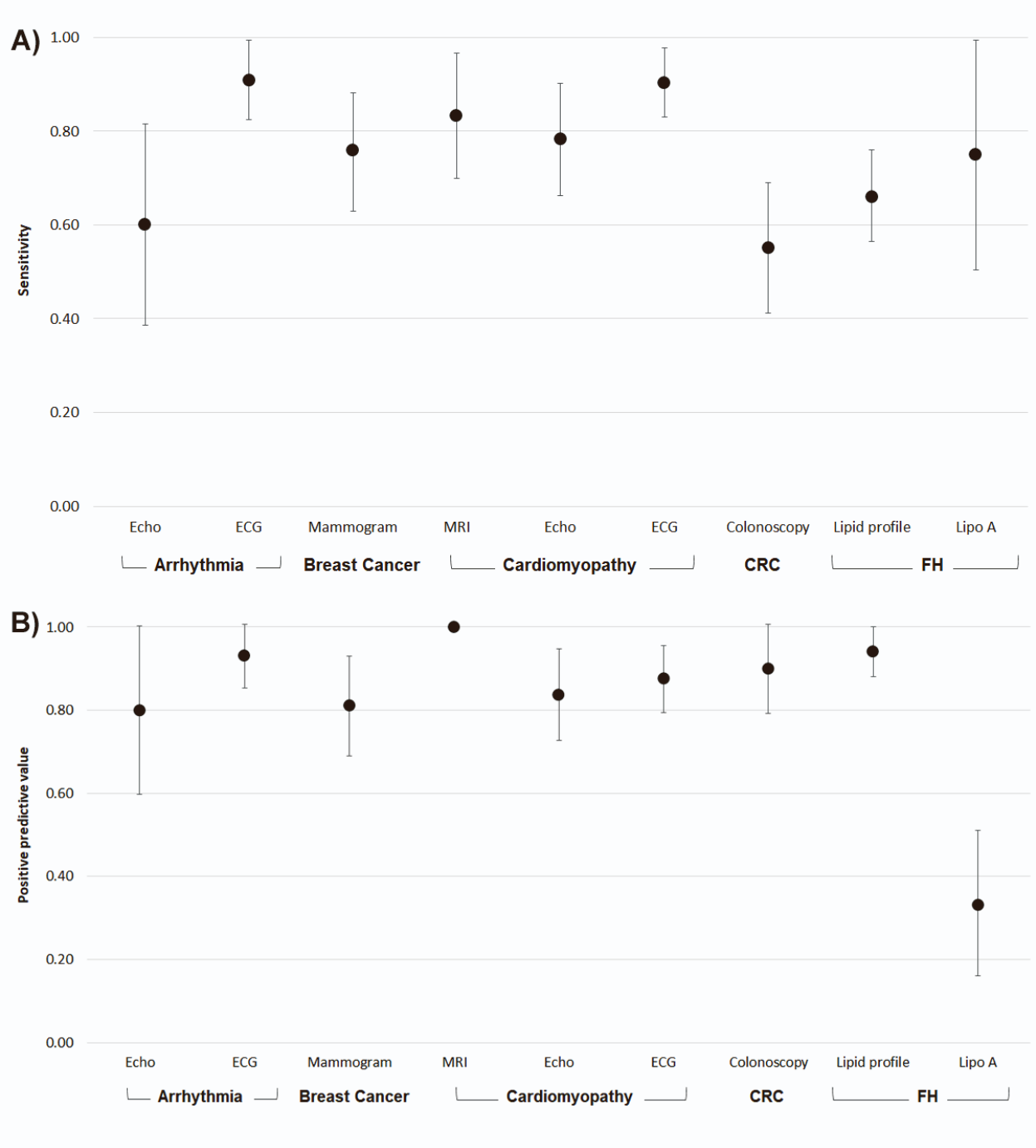

Figure S1. Accuracy of utilizing CPT codes to assess outcomes compared to manual chart review. A) Sensitivity and B) positive predictive value when comparing HI-TAG CPT codes to manual abstraction for tests with >10 instances. Bars represent 95% confidence intervals. CRC: Colorectal cancer; FH: familial hypercholesterolemia, ECG: electrocardiogram, MRI: magnetic resonance imaging, Echo: Echocardiogram.

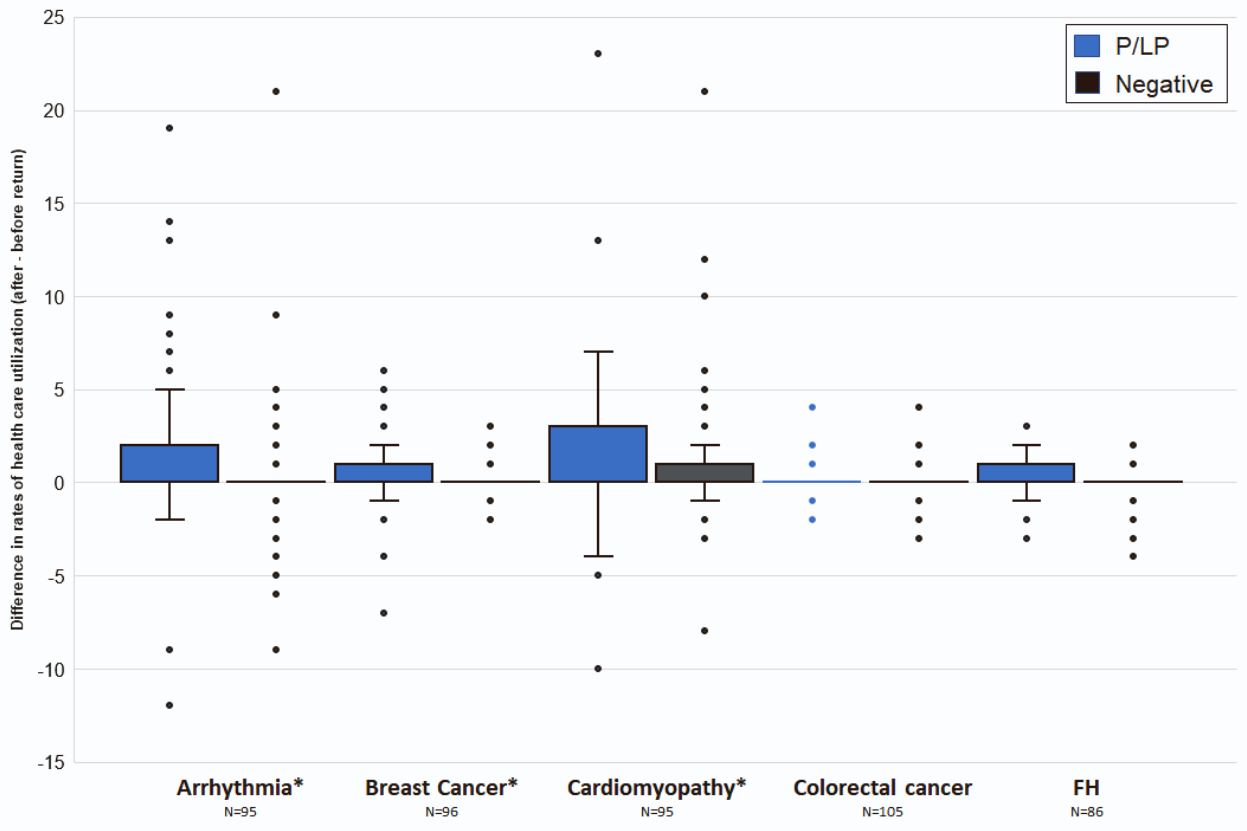

Figure S2. Differences in frequency of health care utilization in participants before and after return of results. When the change in services among participants with P/LP results were compared to those without a variant**,** there were significantly higher rates in the P/LP group for three (arrhythmia $p < 0.0001$, breast cancer $p = 0.006$, cardiomyopathy $p = 0.038$) a marginally significant difference in colorectal cancer ($p = 0.052$) and a non-significant difference for FH ($p > 0.05$) at one year post return. Box represents interquartile range (IQR), with whiskers representing varibility outside the quartiles, and outliers represented as dots. Data shown limited to 5 to 95 percentiles of rates. IQR for colorectal cancer and FH are 0. FH: familial hypercholesterolemia, * indicates $p < 0.05$.

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