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ARTICLE

Genetic findings and health care utilization among individuals undergoing population genomic screening for actionable hereditary disorders

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ABSTRACT

Purpose: Genomic screening (GS) can identify the risk of medically actionable, monogenic conditions in individuals who would otherwise not be considered for genetic testing. The yield of pathogenic variants and associated health care utilization among at-risk individuals have not been well-studied in real-world settings.

Methods: Physicians ordered GS panels for up to 167 genes. Calculations included the positive yield overall and for 81 genes on the American College of Medical Genetics and Genomics' secondary findings list. Health care utilization and costs were analyzed using insurance claims from 12 months before and after the genetic test results.

Results: Among 50,063 individuals, 8.6% had pathogenic/likely pathogenic variants conferring monogenic risk. Relevant health care utilization was higher in individuals with positive results than in those with non-positive results. There was a small but significant increase in median cost of all-cause health care utilization post-test compared with pre-test in participants with positive ($340 vs $215, $P = .02$) but not negative results ($308 vs $252, $P = .12$).

Conclusion: These findings suggest that GS in real-world settings can identify at-risk individuals and prompt intervention without significantly increasing health care costs or utilization.

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Introduction

The Centers for Disease Control and Prevention (CDC) has designated three conditions—hereditary breast and ovarian cancer (MIM 604370), Lynch Syndrome (LS) (MIM 120435), and familial hypercholesterolemia (FH) (MIM 143890)—as Tier 1 conditions for cascade testing within families, and others have proposed these as a starting point for population genomic screening (GS)[1] to identify the estimated 1% to 2% of the US population harboring pathogenic or likely pathogenic variants (PVs) in genes associated with these conditions.[2-5] A 2018 report similarly recommended screening for ten genes, including *BRCA1* (HGNC:1100), *BRCA2* (HGNC:1101), *MLH1* (HGNC:7127), *MSH2* (HGNC:7325), *MSH6* (HGNC:7329), *PMS2* (HGNC:9122), *EPCAM* (HGNC: 11529), *LDLR (*HGNC:6547), *APOB (*HGNC:603), and *PCSK9* (HGNC:20001) that are associated with these conditions.[1] GS allows identification of individuals who are at risk for developing these conditions, including those without significant family histories, to allow for early intervention strategies that can reduce morbidity and mortality.

In contrast to the limited number of genes related to the CDC Tier 1 conditions, recent guidance from the American College of Medical Genetics and Genomics (ACMG) lists a minimal set of 81 genes for which clinical laboratories should analyze and report PVs as clinically actionable secondary findings (SF) when performing clinical exome or genome sequencing.[6] The ACMG SF gene list increased from 56 to 81 between 2013 and 2023 and is expected to be updated periodically, resulting in larger sets of genes associated with clinically actionable disorders.[6-9] The positive screening yield from a panel of 59 genes from the ACMG SF v2.0 guidelines[8] ranged from 1.5% to 2.5%.[10,11] Studies that evaluated additional genes beyond the 59 genes listed by the ACMG have reported positive findings in 3.5% to 8.3% of individuals screened for ~75 genes,[12,13] 3.4% of individuals screened for the newer ACMG list of 81 genes,[14] and in up to 16% of individuals screened for as many as 432 genes.[15,16]

The efficacy of GS programs depends not only on the positive screening yield but also on the affordability of and reimbursement for testing, the follow-up care, and the short- and long-term outcomes after positive screening results.[17] The cost-effectiveness of GS is influenced by the extent to which at-risk individuals adopt guideline-recommended risk-reducing and disease management strategies and avoid inappropriate or unnecessary health care utilization.[5,18] A recent multi-institutional study by the Electronic Medical Recores and Genomics (eMERGE) consortium demonstrated that individuals with positive GS results accessed clinical services more frequently, albeit with modestly higher costs than those who received negative results,[19] whereas several modeling studies have indicated that screening for highly penetrant monogenic disorders may be cost-effective when applied to young individuals and using approaches that evaluate the risk for several disorders in a single genetic test.[20-22]

Most of the published data on the uptake of GS, positive GS yield, subsequent health care utilization, and the costs of population screening are obtained from research studies rather than real-world settings. In this study, we generated GS results for a cohort of 50,063 individuals across various health care systems who underwent physician-ordered proactive screening of up to 167 genes associated with clinically actionable monogenic disorders. Here, in this article, we describe the prevalence of clinically significant variants in these individuals and, by linking positive results to real-world health insurance claims, how GS-informed risk-reducing strategies affected the costs of health care utilization before and after the return of positive results.

Materials and Methods

Study cohort

Individuals ≥18 years who underwent physician-ordered GS at a single commercial laboratory (Invitae Corp [now Labcorp], San Francisco, CA) were considered eligible for this retrospective study. Participants were self-referred for genetic testing in the setting of executive health or wellness clinic offerings. Genetic testing was performed between April 2017 and March 2025. The use of de-identified genetic data was approved by the WIRB-Copernicus Group (WCG) Institutional Review Board (study number 1162292). Clinical and demographic data were extracted from the test requisition form. Family and personal history of cancer and cardiovascular disease were determined by a programmatic search of diagnostic codes and the testing indication and family history free text provided by participants or clinicians on the test requisition form. Free-text keywords and diagnostic codes associated with family and personal history were identified by a medical geneticist and a genetic counselor. To protect participant privacy, free text fields were not linked to claims information, so this level of review was not available for the health care utilization and cost cohort.

Next-generation sequencing, variant calling, and clinical classification of variants

All DNA sequencing, variant detection, and variant classification were performed at a single clinical laboratory, as previously described.[16,23-27] Gene selection for the GS panels has been previously described.[16] Variants of uncertain significance were not reported, per professional

recommendations.[8] Sequence variants were analyzed and reported using the GRCh37/hg19 human genome assembly (GenBank accession GCF_000001405.13).

Return of results

Genetic test results were returned directly to the ordering physician and the tested individual through secure online portals without automatic integration into electronic health records. Individuals and their physicians were responsible for sharing and documenting genetic findings in medical records and for coordinating any follow-up care based on the results.

Positive yield calculation cohort

Individuals undergoing genetic testing with at least one of four panels (Genetic Health Screen, Cardio Screen, Cancer Screen, and Actionable Disorders) (Supplemental Figure 1) were eligible for inclusion, regardless of their personal or family history of disease.

Positive yield was calculated from the reported findings after excluding low-penetrance variants, increased risk alleles, potentially positive results (cases where two PVs were identified in the same gene associated with autosomal recessive inheritance, but phase could not be determined), single PVs in genes associated with autosomal recessive inheritance patterns (heterozygote-only results), and *F5* PVs[28] (Figure 1). For consistency with the ACMG recommendations, in the positive yield subanalysis of the 81 genes in the ACMG SF v3.2,[6] the NC_000006.11:g.26093141G>A [NM_000410.4:c.845G>A; p.(Cys282Tyr)] variant of *HFE* (HGNC:4886) was included, despite being low penetrance, and non-truncating pathogenic or likely pathogenic *TTN* (HGNC:12403) variants were also excluded (Figure 1).

Health care utilization and costs cohort

Individuals were eligible for health care utilization and cost analyses if they underwent GS, had claims in the Komodo Healthcare MapTM database (Komodo Healthcare, New York, NY), and maintained continuous health insurance coverage for 12 months before and after receiving their genetic test results. Out of 50,063 individuals, 4144 (8.3%) met the above mentioned criteria. Genetic test data were securely linked to US insurance claims data using unique tokens, excluding protected health information. Individuals with positive results were matched to at least one individual without positive findings (one-to-many matching) based on sex, ancestry, test panel type, and age ±2 years (Supplemental Figure 2).

Health care data for the 12 months before and after the return of genetic testing results (index date) were extracted using the International Classification of Diseases (ICD) and Current Procedural Terminology (CPT) codes. Amounts billed to insurance were extracted directly from the Komodo Healthcare MapTM using medical claims data and reported per person per year.

Post-test usage of all ICD-10 diagnosis codes and CPT procedure codes between matched groups of participants were compared to evaluate how GS results influenced health care utilization. For each specific code being analyzed, any participant who had that code recorded before the study period was excluded, ensuring that only new occurrences of diagnoses or procedures were captured. This exclusion was applied on a per-code basis: if a participant had a given ICD-10 or CPT code before receiving the test result, the participant was excluded from the analysis for that specific code only, but remained in the analytic set for other codes. Consequently, denominators vary across codes.

Hazards ratios were calculated for the appearance of each ICD-10 and CPT code after the test was returned. To ensure robustness and reduce the risk of false-positive results, a stringent significance threshold of $P < .001$ was adopted,[29] and all Hazards ratio results that met the threshold are reported.

Statistical analysis

All analyses were performed using R Statistical Software (v4.2.1; R Core Team 2022). Tests for differences in means and medians were conducted using paired *t*-tests and Mann-Whitney U tests, respectively. χ^2-test was used to compare categorical variables. A post-hoc power analysis was conducted using two-sample t-test with unequal group sizes to determine the minimum detectable effect sizes at 80% power and $\alpha = 0.05$.

Results

Positive yield calculation

Among the 50,362 individuals undergoing voluntary physician-ordered GS, 299 were known to have previously tested positive for a variant included in the screening panels used here and were excluded from further analysis. Among the remaining 50,063 individuals, a majority were female (58.8%) or White (56.2%); the mean age at the time of testing was 48.1 years (Table 1).

A total of 20,470 (40.9%) individuals reported GS findings. After excluding heterozygote-only results (ie, heterozygous for a single PV in a gene associated with an autosomal recessive disorder), 8157 (16.3%) had reported findings (Figure 1). Following the exclusion of low-penetrance variants, increased-risk alleles, potentially positive results, and *F5* variants, there were 4293 (8.6%) individuals with positive results, and the majority had a PV in a single gene (4109, 95.7%), followed by 180 (4.2%) and 4 (0.1%) individuals who had two and three PVs in different genes, respectively. Among individuals with a positive result, genes with the highest frequency of PVs were *BRCA2* (413, 0.8%), *CHEK2*

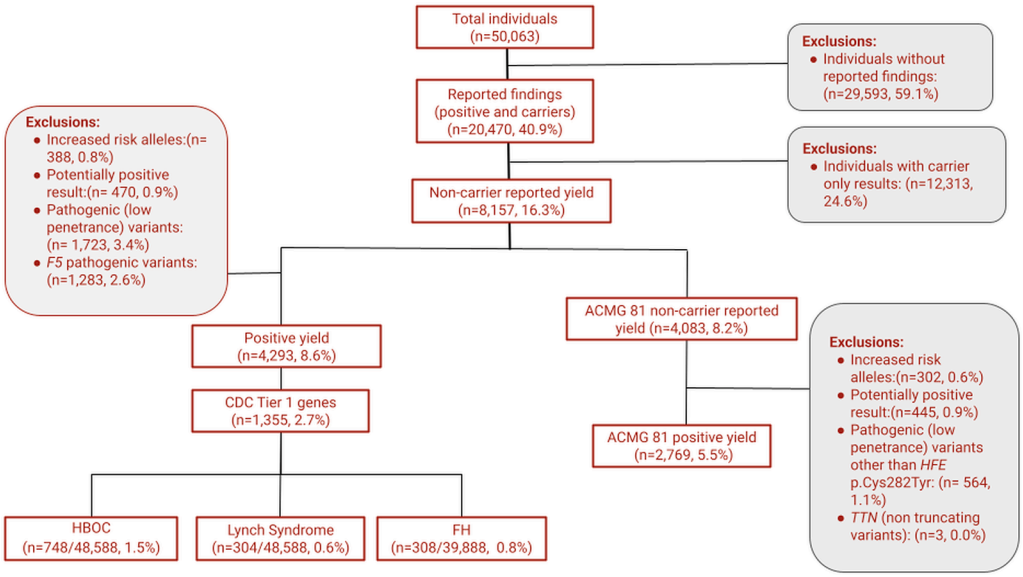

Figure 1 Diagnostic yield across genomic screening panels and gene subsets. Among 50,063 individuals tested (58.8% female, 56.2% White; mean age 48.1 years), family or personal history of cancer was noted for 26.7% (females) and 3.0% (White individuals) respectively, and family or personal history of cardiac conditions for 35.1% (females) and 1.2% (White individuals) respectively. Approximately one-fifth of tests were performed for individuals living outside the United States. Data are shown for the combined cohort (all individuals tested), cancer screening cohort, and cardiovascular screening cohort. Results are stratified by: 1) overall reportable findings before and after exclusion of carrier status; 2) positive yield after sequential exclusion of variants not considered clinically actionable; 3) yield for genes included in the ACMG SF v3.2 (81 genes) and v2.0 (59 genes) recommendations after applying the ACMG-specific inclusion criteria; 4) yield for CDC Tier 1 conditions, including hereditary breast and ovarian cancer (HBOC), Lynch syndrome, and familial hypercholesterolemia (FH); and 5) positive findings categorized by clinical area (cancer; cardiovascular; and other conditions including metabolic, autoinflammatory, neuromuscular, ocular disorders, and surgical risk). Denominators vary by panel as not all individuals were tested for all genes. Percentages are calculated based on the number of individuals tested for each specific gene set.

(HGNC:16627) (348, 0.8%), *BRCA1* (335, 0.7%), *ATM* (HGNC:795) (274, 0.6%), and *LDLR* (204, 0.5%) (Supplemental Figure 3). Positive GS results for CDC Tier 1 conditions were observed in 1355 (2.7%) individuals and for the ACMG SF v.3.2 list in 2769 (5.5%) individuals. Of the ACMG v3.2 genes that were not included in the ACMG SF v2.0 gene list, *TTN* (73, 0.4%), *HFE* (104, 0.3%), and *PALB2* (HGNC:26144) (99, 0.2%) had the highest rates of PVs (Supplemental Figure 4). The highest frequency of positive results was found in cancer-related genes (5.5%), followed by cardiovascular disease-related genes (4.0%), and in 20 genes that were unique to the Genetic Health Screen panel (0.9%) (Table 2). Per-gene counts and frequencies for all tested genes are provided in Supplemental Table 1.

Participants with a positive result were more likely to have either a family history of cancer (1292, 30.1% vs 8193, 27.7%; $P = .001$) or cardiovascular disease (1928, 44.9% vs 8385, 28.4%; $P < .001$) compared with participants without reported GS findings. There was no statistically significant difference between participants with positive result and those without reported GS findings in the rates of personal history of cancer (150, 3.5% vs 1,042, 3.5%; $P = .948$) or cardiovascular disease (54, 1.3% vs 321, 1.1%; $P = .356$).

Health care utilization and cost

Of the 50,063 individuals in the overall cohort, 4144 (8.3%) had available claims data in the Komodo Healthcare MapTM database and continuous health care coverage for the 12 months before and after GS. Of the individuals with available claims data, 783 with positive GS results were matched to 3361 without positive findings (Supplemental Figure 2). A majority of these 4144 individuals were female (69.5%) or White (73.1%) and had a mean age of 50.8 years at the time of testing (Table 1). A total of 841 PVs from 73 genes were detected, with 50 of 783 (6.4%) and 4 of 783 (0.5%) individuals harboring PVs in two and three genes, respectively. The health care utilization cohort differed significantly from the overall cohort across demographic variables. Compared with the overall cohort, the claims subset had higher proportions of White individuals (73.1% vs 56.2 %; $\chi^2 = 658.34$; $P < .001$) and female individuals (69.5% vs 58.8 %; $\chi^2 = 198.0$; $P < .001$), was older (mean age 50.8 vs 48.1 years; $P < .001$), and showed marked differences in panel selection, with overrepresentation of the Gene Actionable Disorder Panel (28.1% vs 9.8%; $\chi^2 = 1660$; $P < .001$).

Table 1 Demographic characteristics of the full cohort of individuals undergoing proactive genetic testing and the subset for whom health claims data was available

Patient Demographics	Overall Cohort $N = 50,063$	Health Care Utilization and Cost Cohort $N = 4144$
Self- or clinician-reported ancestry		
Ashkenazi Jewish	1010 (2.0)	12 (0.3)
Asian	4628 (9.2)	149 (3.6)
Black/African American	1090 (2.2)	53 (1.3)
Hispanic	2353 (4.7)	304 (7.3)
Multiple ancestries	3084 (6.2)	132 (3.2)
Unknown/other	9776 (19.5)	463 (11.2)
White	28,122 (56.2)	3031 (73.1)
Age ranges		
<20	186 (0.4)	4 (0.1)
20-29	4281 (8.6)	144 (3.5)
30-39	10,795 (21.6)	616 (14.9)
40-49	12,537 (25.0)	1031 (24.9)
50-59	11,019 (22.0)	1331 (32.1)
60-69	7483 (14.9)	824 (19.9)
70-79	3166 (6.3)	182 (4.4)
≥80	596 (1.2)	12 (0.3)
Average age (y)		
Mean (SD)	48.1 (14.0)	50.8 (11.6)
Median (Q1, Q3)	47 (37, 58)	52 (42, 59)
Range	18-90	18-81
Gender		
Female	29,418 (58.8)	2881 (69.5)
Male	20,645 (41.2)	1263 (30.5)
Panel ordered		
Invitae Genetic Health Screen	33,406 (66.7)	2407 (58.1)
Invitae Cancer Screen	10,175 (20.3)	531 (12.8)
Invitae Cardio Screen	1475 (2.9)	40 (1.0)
Invitae Cardio Screen and Invitae Cancer Screen	120 (0.2)	0 (0.0)
Invitae Gene Actionable Disorder Panel	4887 (9.8)	1166 (28.1)
Number of genes analyzed		
56-83	16,537 (33.0)	1737 (41.9)
130-142	998 (2.0)	0 (0.0)
146-157	16,663 (33.3)	1190 (28.7)
167	15,865 (31.7)	1217 (29.4)
Non-US	9828 (19.6)	0 (0.0)
Family history		
Family history of cancer	13,388 (26.7)	NA
Family history of cardio	17,593 (35.1)	NA
Personal history		
Personal history of cancer	1501 (3.0)	NA
Personal history of cardio	594 (1.2)	NA

NA, not applicable; *Q*, quartile.

Note: Information provided is self-reported or clinician-reported ancestry. Age represents the age of an individual at the time of testing. Values are presented as *n* (%), unless otherwise specified.

The median cost of all-cause health care utilization for 4144 individuals did not differ significantly within 12 months post-testing compared with the median cost 12 months pre-testing ($314 vs $246; $P = .30$). However, when analyzed by genetic testing results, median health care costs were higher after the return of test results in 783 individuals with positive results ($340 vs $215; $P = .02$) but not for the 3361 individuals with non-positive results ($308 vs $252; $P = .12$) (Supplemental Figure 5). In contrast, there were no significant differences observed between median pre-test costs ($P = .22$) and median post-test costs ($P = .37$) between individuals with positive and non-positive results.

After excluding 89 participants with pre- or post-period costs in the top or bottom 1%, a difference-in-difference analysis comparing pre-to-post cost changes revealed no

Table 2 Yield of positive genomic screening results by panel type and gene categories

Findings	Combined Cohort $N = 50,063$	Cancer Cohort $N = 48,588$	Cardio Cohort $N = 39,888$
Individuals with reportable findings (positive and carrier results)	20,470 (40.9)	20,235 (41.6)	19,242 (48.2)
Individuals with reportable findings (excluding carrier results)	8157 (16.3)	7937 (16.3)	7181 (18.0)
Positive yield after excluding increased risk alleles, potentially positive results, pathogenic (low penetrance) alleles, and *F5* pathogenic variants	4293 (8.6)	4158 (8.6)	3477 (8.7)
Findings for 81 genes prescribed by ACMG SF v3.2			
Individuals with reportable findings in the 81 ACMG SF v3.2 genes (excluding carrier results)	4083 (8.2)	3955 (8.1)	3534 (8.8)
Positive yield after excluding increased risk alleles, potentially positive results, *TTN* non-truncating variants, and pathogenic (low penetrance) alleles other than *HFE* p. (Cys282Tyr)	2769 (5.5)	2641 (5.4)	2296 (5.8)
Findings for 59 genes prescribed by the ACMG SF v2.0			
Individuals with reportable findings in the 59 ACMG SF v2.0 genes (excluding carrier results)	2704 (5.4)	2594 (5.3)	2197 (5.5)
Positive yield after excluding increased risk alleles, potentially positive results, and pathogenic (low penetrance) alleles	2402 (4.8)[a]	2292 (4.7)	1970 (4.9)
Findings in CDC Tier 1 genes (N/#tested [% tested])			
Positive findings in genes associated with HBOC, FH, and LS	1355/50,063 (2.7)	1330/48,589 (2.7)	970/39,887 (2.4)
HBOC findings only (*BRCA1*, *BRCA2*)	748/48,588 (1.5)	748/48,588 (1.5)	444/38,413 (1.2)
LS findings only (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*)	304/48,588 (0.6)	304/48,588 (0.6)	222/38,413 (0.6)
FH findings only (*LDLR*, *APOB*, and *PCSK9*)	308/39,888 (0.8)	283/38,413 (0.7)	308/39,888 (0.8)
Positive findings by clinical area (no of positive individuals/no. of tested individuals [% positive])			
Cardio	1588/39,888 (4.0)	1453/38,413 (3.8)	1588/39,888 (4.0)
Cancer	2687/48,588 (5.5)	2687/48,588 (5.5)	1871/38,413 (4.9)
Other	348/38,293 (0.9)	348/38,293 (0.9)	348/38,293 (0.9)
Autoinflammatory disorder (*MEFV*)	7/15,865 (0.04)	7/15,865 (0.04)	7/15,865 (0.04)
Metabolic disorder (genes including, *ABCD1, ATP7B, BTD, GAA, G6PD, HAMP, HFE, HJV, HMBS, HNF1A, HNF1B, OTC, SERPINA1, SLC40A1,* and *TFR2*)	240/37,348 (0.6)	240/37,348 (0.6)	240/37,348 (0.6)
Neuromuscular disorder (*GCH1*)	11/15,865 (0.1)	11/15,865 (0.1)	11/15,865 (0.1)
Ocular disorder (*RPE65*)	0/15,918 (0)	0/15,918 (0)	0/15,918 (0)
Surgical risk (*RYR1* and *CACNA1S*)	102/38,293 (0.3)	102/38,293 (0.3)	102/38,293 (0.3)

ACMG, American College of Medical Genetics and Genomics; *CDC*, Center for Disease Control and Prevention; *FH*, familial hypercholesterolemia; *HBOC*, hereditary breast and ovarian cancer; *LS*, lynch syndrome.

Note: The diagnostic yields across different genomic screening panels and gene subsets. Data are shown for the combined cohort (all individuals tested), cancer screening cohort, and cardiovascular screening cohort. Results are stratified by: 1) overall reportable findings before and after exclusion of carrier status; 2) positive yield after sequential exclusion of variants not considered clinically actionable; 3) yield for genes included in ACMG SF v3.2 (81 genes) and v2.0 (59 genes) recommendations after applying ACMG-specific inclusion criteria; 4) yield for CDC Tier 1 conditions (HBOC, LS, and FH); and 5) positive findings categorized by clinical area (cancer, cardiovascular, and other conditions including metabolic, autoinflammatory, neuromuscular, ocular disorders, and surgical risk). Denominators vary by panel as not all individuals were tested for all genes. Percentages are calculated based on the number of individuals tested for each specific gene set. Values are presented as *n* (%), unless otherwise specified.

[a]Excludes increased risk alleles, potentially positive results, and pathogenic (low penetrance) alleles.

significant difference between participants with positive results (n = 769, mean change +$417) and participants with non-positive results (n = 3286, mean change –$1.8; P = .074). However, restricting this difference-in-difference analysis to genes with established clinical utility revealed significant differences. Participants with a positive result in a gene on the ACMG SF v3.2 list (n = 411) had $743 higher mean costs than those with non-positive results (n = 1975, +$754 vs +$11; P = .009). The largest difference was observed for CDC Tier 1 conditions, including —hereditary breast and ovarian cancer, LS, and FH, where positive results (n = 207) were associated with $1480 higher mean costs than those with non-positive results (n = 1128, mean change +$1423 vs –$57; P < .001). Post-hoc power analysis indicated that our study had 80% power to detect a difference-in-difference of $662.81 in the full matched cohort, $876.82 in the ACMG subset, and $1227.93 for CDC Tier 1 conditions.

The proportions of individuals with positive and non-positive results who did not have relevant Z15.0 (ie, genetic susceptibility to cancer) codes in their records before testing were compared to estimate how many had a Z15.0 code in their medical records after genetic testing (Figure 2). Among individuals with positive LS findings, 21/34 (62%) had at least one Z15-related code post-reporting, compared with only 5/184 (3%) of individuals with non-positive results ($P = 4.7 \times 10^{-16}$). Female individuals with positive results in *BRCA1* or *BRCA2* had significantly higher Z15.0 code usage: 34/36 (94%) had codes added after the return of positive genetic test results compared with 52/676 (8%) of female individuals with non-positive results ($P = 2.2 \times 10^{-16}$). In contrast, 8/25 (32%) of male individuals with positive results in *BRCA1* or *BRCA2* had one or more Z15.0 codes added post-testing compared with 4/94 (4%) of male individuals with non-positive results ($P = 3.8 \times 10^{-4}$). In addition, compared with individuals with non-positive results, those with positive findings in *LDLR*, *APOB (*excluding those with variants associated with hypobetalipoproteinemia), or *PCSK9* genes were significantly more likely to have ICD-10 codes for FH (7/26 vs 1/142; $P = 7.2 \times 10^{-6}$) (Supplemental Figure 6) added after testing, and those with positive findings in *HFE* were significantly more likely to have ICD-10 codes for hemochromatosis (E83.110; 9/85 vs 0/300; $P = 8.8 \times 10^{-7}$) (Supplemental Figure 7). For individuals with positive genetic test results, documentation of these findings in medical records varied significantly, ranging from 10/88 (11%) for those with PVs in *HFE* to 42/61 (69%) for those with PVs in *BRCA1* or *BRCA2*.

Clinical management strategies varied based on the observed risks for specific genetic disorders. Individuals who received positive results in any gene on the cancer-screening panel significantly more often had subsequent ICD-10 codes [e.g., Z4009 encounter for prophylactic removal of other organ; odds ratio = 45.42, 95% CI: 2.40-861.06) and CPT codes (e.g., 43237 esophagogastroduodenoscopy; odds ratio = 28.35, 95% CI: 3.30-243.48) related to clinical management of cancer risk in their claims data than those with non-positive results (Figure 3). Females with positive results in *BRCA1* and *BRCA2* more often appeared to undergo nonprocreative genetic counseling (ICD-10 Z7183; 13/19 vs 87/685; $P = 1.2 \times 10^{-5}$) and prophylactic removal of the ovaries (ICD-10 Z90722; 17/23 vs 76/653; $P = 4.7 \times 10^{-8}$) than those with non-positive results (Supplemental Figure 8). Of note, 6/88 (6.9%) individuals with PVs in *BRCA1* or *BRCA2* had the ICD code for ovarian cancer (ICD-10 C569) added to their claims database after the return of screening results, compared with none among the 686 non-positive individuals; and 2/45 (4.4%) individuals with PVs in LS genes had ICD codes for colon cancer (ICD-10 C182) added after the return of GS results, compared with none among the 198 non-positive individuals. Individuals with positive results in LS genes were also significantly more likely to have post-test anesthesia for lower intestinal endoscopic procedures (CPT 00813); $P = 6.4 \times 10^{-6}$) than those with non-positive results (Supplemental Figure 9).

The results for individuals with positive findings in *BRCA1* or *BRCA2* differed by gender. Although both male and female individuals with positive results were more likely to have Z15.0-related ICD-10 codes added to their medical records after testing than those with non-positive results in these two genes, only female individuals showed significant increases in the use of codes indicating acquired absence of breasts ($P = 1.1 \times 10^{-8}$) or breast reconstruction after mastectomy ($P = 5.1 \times 10^{-7}$) in their medical records compared with non-positive female individuals. Procedural codes associated with initiating hysterectomy, breast MRI, and mastectomy after disclosure of genetic results were more likely to be observed among female individuals with positive results in *BRCA1* or *BRCA2* than among those with non-positive results in these genes (Supplemental Figure 8). In contrast, male individuals with positive results in *BRCA1* or *BRCA2* did not show statistically significant differences in the addition of any CPT procedures compared with matched non-positive male individuals.

Compared with individuals with non-positive results, individuals who received positive results on the cardiac screening panel had a range of changes in their medical records, including new ICD-10 codes associated with activated protein C resistance ($P = 7.4 \times 10^{-13}$) and hypertrophic cardiomyopathy ($P = 1.2 \times 10^{-4}$) (Supplemental Figure 10). Individuals with positive results were also more likely to undergo stress echocardiograms and electrocardiographic monitoring procedures than those with non-positive results (Supplemental Figure 10).

Discussion

In a real-world cohort of 50,063 participants who underwent physician-ordered GS using panels containing up to 167 genes, the overall positive yield was 8.6%. These

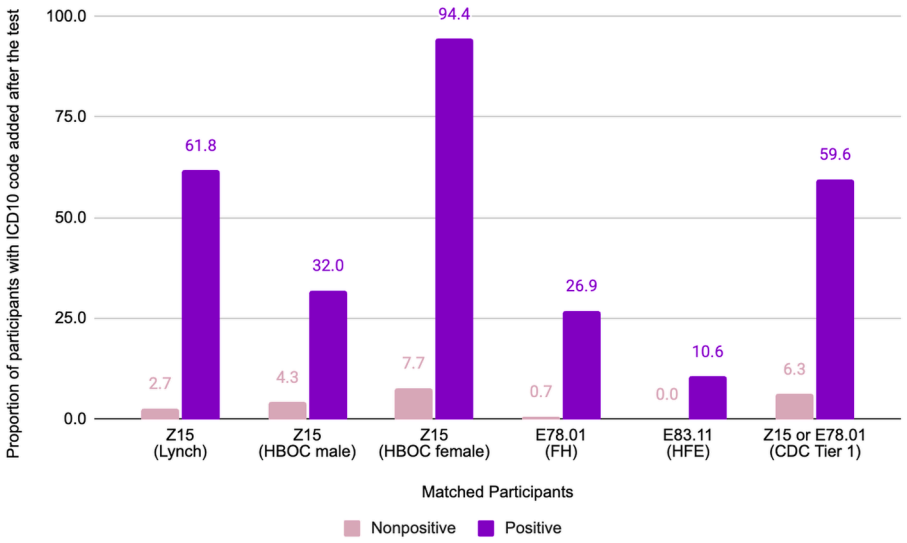

Figure 2 Proportions of participants with ICD-10 codes for genetic susceptibility added after return of genetic test results. Participants with positive genetic test results compared with participants with non-positive genetic test results who had no relevant ICD-10 codes before testing. Bars represent the percentage of participants who received their first genetic condition-related ICD-10 code following genomic screening. Data are stratified by genetic conditions, including Lynch syndrome (Lynch), hereditary breast and ovarian cancer (HBOC), familial hypercholesterolemia (FH), hereditary hemochromatosis (HFE), and test result (positive vs matched non-positive). The CDC Tier 1 category includes participants with either Z15.0 or E78.01 codes. For Lynch syndrome and HBOC, any Z15.0-related code was included (e.g., Z15.01, Z15.02), while exact code matches were required for FH (E78.01) and HFE (E83.11). *ICD-10*, International Classification of Diseases 10th revision.

individuals had actionable genetic findings for which there were published guidelines or recommendations for clinical management approaches to prevent or delay disease onset or to diagnose and treat disease early. This study used large-scale real-world data from physician-directed GS at a clinical laboratory to evaluate rates of positive results based on the ACMG 81-gene list, and to assess health care utilization and associated costs related to GS. Our study indicates that identification of positive GS findings may stimulate changes to clinical management, and it does not significantly affect health care costs immediately after GS. An increase in post-testing health care costs was observed only for individuals with positive GS results.

Previous studies that examined GS results related to the ACMG SF v2.0 list of 59 genes found positive rates ranging from 1.5% to 3.1%.[10,11,30] In our study, the yield of positive results with the current list of 81 genes recommended by the ACMG was 5.5%. The positive rate in our study was higher than the recently reported rate of 3.4% by the Geisinger MyCode Community Health Initiative, possibly because[14] MyCode study enrolled all-comer participants regardless of their phenotype or family history; whereas, our study cohort consisted of individuals who voluntarily chose available GS options in consultation with their health care providers. These individuals may represent a self-selected cohort with a higher prior genetic risk for hereditary disease due to personal or family history. For example, for participants with positive findings in a gene on the ACMG 81-gene list, our study cohort had a higher proportion of positive findings in genes associated with cancer compared with MyCode cohort (47.3% vs 39.7%, $P < .001$).[14]

The list of genes included in GS continues to change. Hemochromatosis (MIM 235200) is an example of a genetic condition that justifies continually expanding the list of genes for GS, which was not initially included in GS recommendations from professional societies or public health organizations. Hemochromatosis is often diagnosed after irreversible organ damage has occurred,[31] and for which early identification of at-risk individuals who are homozygous for the common *HFE* [NM_000410.4:c.845G>A (p.Cys282Tyr)] allele allows effective treatment to reduce iron overload.[32] In our study, 104/33,459 (0.3%) individuals were homozygous for p.(Cys282Tyr), similar to the frequency identified by the Geisinger MyCode Community Health Initiative (201/86,601, 0.2%).[33] Similarly, 172 individuals in our study were positive for actionable variants in *PALB2* and *TTN*, which would have been missed if earlier iterations of the ACMG gene list were used for GS. Because these individuals are at risk for cancer or cardiovascular disease, positive screening results allow for appropriate clinical management strategies to improve outcomes.

In addition to the 390 individuals with PVs in genes newly added to the ACMG gene list, 1720 (3.4%) had positive results in other genes that were not in any version of the ACMG gene lists. Among these other genes, the highest rates of positive GS results were for *CHEK2* (0.8%), *ATM* (0.6%), *MITF* (0.5%), and *G6PD* (0.5%). As risk and penetrance estimates and medical actionability

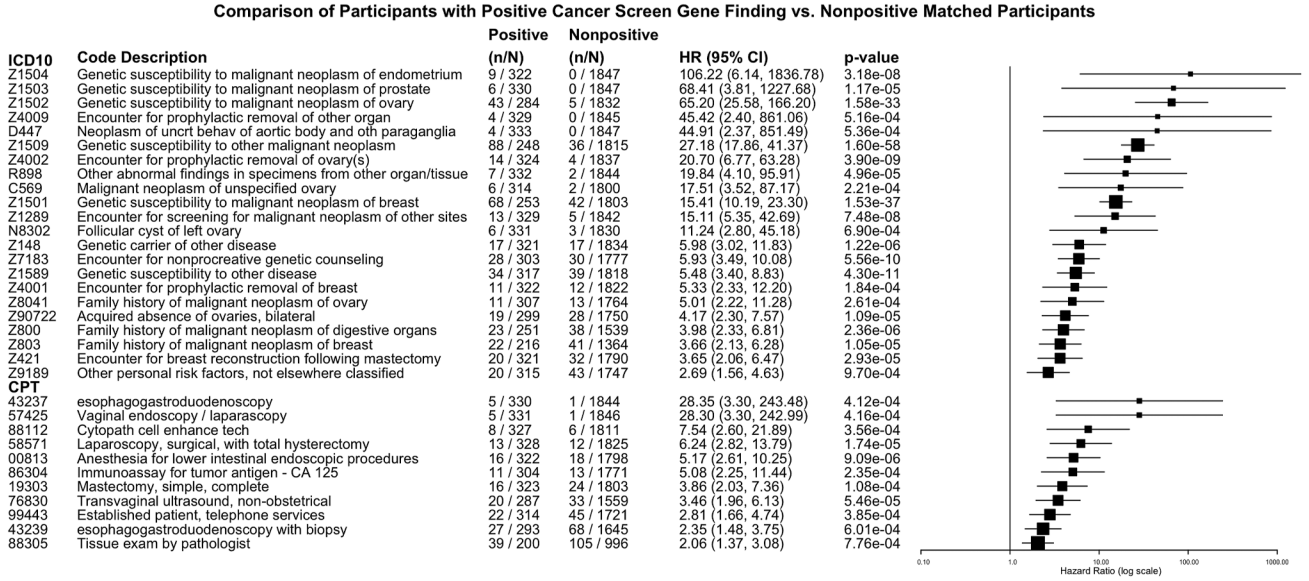

Figure 3 Hazard ratios for first observation of diagnosis and procedure codes within 12 months following positive cancer screening panel results. Forest plot comparing health care utilization between individuals with positive cancer screening gene findings (*n* varies by code) and matched non-positive controls (*n* varies by code). Only participants without prior documentation of each specific code were included in the analysis for that code. The left panel lists International Classification of Diseases 10th revision (ICD-10) diagnosis codes and Procedural Terminology (CPT) codes with descriptions and the number of positive and non-positive individuals analyzed. The center panel shows hazard ratios (HRs) with 95% confidence intervals (CIs) and *P* values. The right panel displays the forest plot with HRs on a logarithmic scale, where values >1 indicate increased likelihood of code documentation in positive versus non-positive individuals. Square size reflects the precision of each estimate. All codes shown met the significance threshold of $P < .001$.

improve for genes associated with cancer, cardiovascular, and other hereditary conditions, the ACMG gene list is expected to expand further,[34] allowing more individuals with positive results to consider medical interventions to prevent or delay disease onset, thereby improving health.[35]

Our study examined GS results that were returned to individuals without direct electronic health record integration. Most individuals with positive results had appropriate ICD-10 codes applied, indicating successful incorporation into their health care. This compares favorably to other programs: the Geisinger MyCode Initiative, with coordinated staff support, achieved 70% clinical management changes for Tier 1 conditions,[35] whereas the Healthy Nevada Project, relying on participant initiative, created management plans for 55.3% of those who shared results.[36] In our cohort, participants with positive results showed significantly higher uptake of clinical management strategies and relevant ICD coding compared with those who had non-positive results, demonstrating that GS effectively identifies at-risk individuals and promotes appropriate clinical interventions without increasing unnecessary health care utilization in those with non-positive results.

In our study, there was a significant, though small, median increase in costs for individuals with positive results after the return of positive genetic test results. Importantly, we detected no significant increase in health care costs after the return of results for individuals with non-positive results. These findings were similar to those detected in the eMERGE trial, with an average increase of $180.72 in individuals with positive results and no significant increase in those without positive results.[19] GS does not appear to lead to increased health care costs in the majority of individuals, but additional studies are needed to determine whether short-term increased health care costs in individuals with positive results translate into long-term cost savings for the health care system as a result of fewer medical interventions.

This study shares limitations with prior work.[16] Pre-GS treatments or risk-reducing strategies may have obscured differences in health care utilization. Personal and family history were unavailable for the claims analysis, preventing evaluation of their impact. The health care utilization cohort overrepresented White individuals, females, adults aged between 50 to 69 years, and Gene Actionable Disorder Panel recipients, reflecting U.S. insurance patterns and limiting generalizability; underrepresentation of younger adults and minorities may underestimate their GS responses. Nonetheless, alignment with eMERGE suggests that modest cost increases are consistent across populations, and the cohort's stable insurance coverage is relevant for policy and reimbursement decisions. Second, GS conditions have largely been studied in clinically affected populations, and recent literature questions whether penetrance, expressivity, and age of onset differ in healthy populations,

raising concerns about overdiagnosis for individuals who may never develop disease.[37-39] Estimating true health care costs is challenging because charges often exceed actual costs or reimbursement, which vary widely by payer.[40] Our cost findings apply to the U.S. health care system, and utilization and costs differ across countries. Finally, the one-year post-testing follow-up may not capture longer-term clinical actions, which potentially limits observed procedure rates.

As a result of increasing access and awareness, GS to assess personal risk for inherited genetic conditions is likely to expand. Integrated delivery networks, employers, insurance companies, and nationalized health care systems are exploring the potential for GS to reduce health care costs on a large scale and improve longevity for people in their care. Large population studies, such as the UK Biobank, AllofUs in the US, or Precision Health Research, Singapore (PRECISE), may help us understand the penetrance of disorders typically included in GS and in diverse populations. Aggregated data from such studies have further encouraged the launch of GS programs in public health and commercial settings. Although our study contributes an important piece to this picture, additional studies are necessary to evaluate downstream costs, for example, through important initiatives such as eMERGE and based on other real-world datasets.

Data Availability

When not prohibited by participant permissions or privacy laws, the de-identified individual data that underlie the results reported in this article will be made available to researchers. Researchers will be asked to submit a short proposal outlining objectives, research questions, and analytical methods, and to submit Institutional Review Board approval or determination of exempt status or nonhuman subjects research. For more information on how to access the Invitae data, please contact the corresponding author.

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Author Contributions

Conceptualization: R.N., S.Aradhya, T.E., S.Aguilar; Data Curation: J.G., E.M.R.; Formal analysis: J.G., E.M.R.; Investigation: J.G., E.M.R.; Methodology: J.G., E.M.R., R.N., S.Aradhya; Project administration: T.E., S.Aguilar, S.Aradhya; Supervision: R.G., R.N., S.Aradhya, T.E., S.Aguilar; Validation: J.G., E.M.R., K.D.C., R.G., P.H.; Visualization: J.G., E.M.R.; Writing-original draft: R.E.E., J.G., S.Aguilar, E.M.R.; Writing-review & editing: T.E., S.Aguilar, E.M.R., R.E.E., K.D.C., P.H., R.G., R.N., S.Aradhya, J.G.

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Ethics Declaration

The use of de-identified genetic data was approved by the WIRB-Copernicus Group (WCG) Institutional Review Board (study number 1162292).

Conflict of Interest

Emily M. Russell and John Garcia are employees of Labcorp (formerly Invitae Corp). Tali Ekstein, Sienna Aguilar and Robert L. Nussbaum are former employees of Invitae Corp (now part of Labcorp). Swaroop Aradhya and Rachel E. Ellsworth are former employees of Invitae Corp (now part of Labcorp), and current employees of Illumina.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2026.102605) contains supplemental material, which is available to authorized users.

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