JAMA Oncology | Original Investigation

Association of Pathogenic Variants in Hereditary Cancer Genes With Multiple Diseases

Chenjie Zeng, PhD, MPH; Lisa A. Bastarache, MS; Ran Tao, PhD; Eric Venner, PhD; Scott Hebbring, PhD; Justin D. Andujar, BS; Sarah T. Bland, MPH, MBA; David R. Crosslin, PhD; Siddharth Pratap, PhD, MS; Ayorinde Cooley, BS; Jennifer A. Pacheco, MS; Kurt D. Christensen, PhD; Emma Perez, MS; Carrie L. Blout Zawatsky, MS; Leora Witkowski, PhD; Hana Zouk, PhD; Chunhua Weng, PhD; Kathleen A. Leppig, MD; Patrick M. A. Sleiman, PhD; Hakon Hakonarson, MD, PhD; Marc. S. Williams, MD; Yuan Luo, PhD; Gail P. Jarvik, MD, PhD; Robert C. Green, MD, MPH; Wendy K. Chung, MD; Ali G. Gharavi, MD; Niall J. Lennon, PhD; Heidi L. Rehm, PhD; Richard A. Gibbs, PhD; Josh F. Peterson, MD, MPH; Dan M. Roden, MD; Georgia L. Wiesner, MD, MS; Joshua C. Denny, MD, MS

Editorial

Supplemental content

IMPORTANCE Knowledge about the spectrum of diseases associated with hereditary cancer syndromes may improve disease diagnosis and management for patients and help to identify high-risk individuals.

OBJECTIVE To identify phenotypes associated with hereditary cancer genes through a phenome-wide association study.

DESIGN, SETTING, AND PARTICIPANTS This phenome-wide association study used health data from participants in 3 cohorts. The Electronic Medical Records and Genomics Sequencing (eMERGEseq) data set recruited predominantly healthy individuals from 10 US medical centers from July 16, 2016, through February 18, 2018, with a mean follow-up through electronic health records (EHRs) of 12.7 (7.4) years. The UK Biobank (UKB) cohort recruited participants from March 15, 2006, through August 1, 2010, with a mean (SD) follow-up of 12.4 (1.0) years. The Hereditary Cancer Registry (HCR) recruited patients undergoing clinical genetic testing at Vanderbilt University Medical Center from May 1, 2012, through December 31, 2019, with a mean (SD) follow-up through EHRs of 8.8 (6.5) years.

EXPOSURES Germline variants in 23 hereditary cancer genes. Pathogenic and likely pathogenic variants for each gene were aggregated for association analyses.

MAIN OUTCOMES AND MEASURES Phenotypes in the eMERGEseq and HCR cohorts were derived from the linked EHRs. Phenotypes in UKB were from multiple sources of health-related data.

RESULTS A total of 214 020 participants were identified, including 23 544 in eMERGEseq cohort (mean [SD] age, 47.8 [23.7] years; 12 611 women [53.6%]), 187 234 in the UKB cohort (mean [SD] age, 56.7 [8.1] years; 104 055 [55.6%] women), and 3242 in the HCR cohort (mean [SD] age, 52.5 [15.5] years; 2851 [87.9%] women). All 38 established gene-cancer associations were replicated, and 19 new associations were identified. These included the following 7 associations with neoplasms: *CHEK2* with leukemia (odds ratio [OR], 3.81 [95% CI, 2.64-5.48]) and plasma cell neoplasms (OR, 3.12 [95% CI, 1.84-5.28]), *ATM* with gastric cancer (OR, 4.27 [95% CI, 2.35-7.44]) and pancreatic cancer (OR, 4.44 [95% CI, 2.66-7.40]), *MUTYH* (biallelic) with kidney cancer (OR, 32.28 [95% CI, 6.40-162.73]), *MSH6* with bladder cancer (OR, 5.63 [95% CI, 2.75-11.49]), and *APC* with benign liver/intrahepatic bile duct tumors (OR, 52.01 [95% CI, 14.29-189.29]). The remaining 12 associations with nonneoplastic diseases included *BRCA1/2* with ovarian cysts (OR, 3.15 [95% CI, 2.22-4.46] and 3.12 [95% CI, 2.36-4.12], respectively), *MEN1* with acute pancreatitis (OR, 33.45 [95% CI, 9.25-121.02]), *APC* with gastritis and duodenitis (OR, 4.66 [95% CI, 2.61-8.33]), and *PTEN* with chronic gastritis (OR, 15.68 [95% CI, 6.01-40.92]).

CONCLUSIONS AND RELEVANCE The findings of this genetic association study analyzing the EHRs of 3 large cohorts suggest that these new phenotypes associated with hereditary cancer genes may facilitate early detection and better management of cancers. This study highlights the potential benefits of using EHR data in genomic medicine.

JAMA Oncol. doi:10.1001/jamaoncol.2022.0373
Published online April 21, 2022.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Joshua C. Denny, MD, MS, National Human Genome Research Institute, National Institutes of Health, 50 South Dr, Bethesda, MD 20894 (joshua.denny@nih.gov).

Understanding the phenotypic consequences of genomic variation is critical to genomic medicine. Uncovering gene-phenotype associations facilitates clinical diagnoses, leads to better treatment, improves prognosis, and provides insights into disease etiology and potential therapeutic targets.[1,2] The application of next-generation sequencing has markedly accelerated the discovery of novel mendelian disease genes and has expanded our knowledge of their characteristic phenotypes. These are epitomized by hereditary cancer genes. Their associated phenotypes have been shown to extend beyond predisposition to cancer.[3-6] However, substantial gaps in knowledge about the spectrum of phenotypes have been noted,[7] suggesting the need for infrastructure and resources to systematically assess gene-phenotype associations.[7,8]

Current approaches to uncover phenotypes include family-based and population-based studies,[9-14] most of which focused on 1 gene and/or 1 trait or similar traits. These studies have fundamentally improved our understanding of diseases and laid foundations for precision medicine.[2] Systematic efforts to collect information on gene-phenotype associations include the Online Mendelian Inheritance in Man (OMIM), which curates knowledge through literature review with decades of efforts.[15,16]

In this study, we hypothesize that additional conditions are associated with hereditary cancer genes. Using an alternative approach, namely, the phenome-wide association study (PheWAS),[17,18] we used the phenotypic data derived from health record data from 3 cohorts, totaling 214 020 participants, to investigate a broad range of phenotypes associated with hereditary cancer genes.

Key Points

Question What is the range of conditions associated with hereditary cancer genes?

Findings This phenome-wide association study used genetic and phenotypic data derived from health-related data from electronic health records in 3 cohorts comprising 214 020 participants to identify 19 new diseases and conditions associated with pathogenic variants in 13 hereditary cancer genes. These new phenotypes included both neoplastic and nonneoplastic diseases.

Meaning These findings contribute to recognition and understanding of the full clinical spectrum of hereditary cancer syndromes, which can facilitate early detection of cancers and better management.

Methods

Two clinical site–based cohorts and 1 population-based prospective cohort were included in this PheWAS. All US-based studies were approved by local institutional review boards, and the UK-based study was approved by relevant research ethnics committees and organizations. Details are provided in eMethods in the Supplement. All participants provided written informed consent according to approved protocols. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) guideline.

Study Populations

The Electronic Medical Records and Genomics Sequencing (eMERGEseq) cohort consisted of 24 956 biobank and prospectively recruited predominantly healthy individuals from 10 clinical sites under the eMERGE network from July 16, 2016, through February 18, 2018.[19] The primary goal of this project was to provide clinical genetic testing and return actionable genetic results to patients.[20] A total of 52% of the participants were unselected and mainly recruited from primary care clinics or identified from biobanks without specific indications, with the others recruited from specific clinics depending on site-specific interests.[19] A detailed description of each site, including enrollment criteria, specific research interest, and enrichment of phenotypes is provided in eMethods in the Supplement. For this study, we removed individuals without *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification* (*ICD-10-CM*), codes in the electronic health records (EHRs). A total of 23 544 individuals were retained for analysis.

The Hereditary Cancer Registry (HCR) at Vanderbilt University Medical Center included all 3794 individuals who received clinical genetic testing for hereditary cancer[21] from May 1, 2012, through December 31, 2019, and who agreed to and consented to be included in this registry. Results of genetic testing were documented in the EHRs. We obtained the EHR data of 3739 individuals through the Research Derivative, a database of clinical and related data derived from EHR systems.[22] Through reviewing clinical records in the HCR, we removed patients who were also participants of the eMERGEseq project (n = 14) and family members of the index patients who were enrolled in the registry owing to cascade testing (n = 483). A total of 3242 patients were retained for analyses.

The UK Biobank (UKB) is a prospective population-based cohort of 500 217 participants recruited from March 15, 2006, through August 1, 2010, who are continuously followed up.[23] We included 200 619 participants with whole-exome sequencing data available at the time of this study. After removing related participants (n = 5007) and those without *ICD-9* and *ICD-10* codes (n = 8378), 187 234 participants were included.

Sequencing and Variant Classification

Germline variant data in the eMERGEseq cohort were obtained from targeted sequencing. Details on the design of the sequencing panel have been described previously.[19] Briefly, this panel consists of a total of 109 genes, including 58 genes from the American College of Medical Genetics and Genomics [ACMG]) actionable finding list and 51 genes nominated by participating sites.[24] The full list of these genes is provided in eTable 1 in the Supplement. Among the 58 genes from the ACMG panel, we selected all genes (n = 25) determined to be associated with cancer phenotypes by the ACMG Secondary Findings Working Group.[24,25] These genes were *APC* (OMIM 611731), *BMPR1A* (OMIM 601299), *BRCA1* (OMIM 113705),

BRCA2 (OMIM 600185), *MEN1* (OMIM 613733), *MLH1* (OMIM 120436), *MSH2* (OMIM 609309), *MSH6* (OMIM 600678), *MUTYH* (OMIM 604933), *NF2* (OMIM 607379), *PMS2* (OMIM 600259), *PTEN* (OMIM 601728), *RB1* (OMIM 614041), *RET* (OMIM 164761), *SDHAF2* (OMIM 613019), *SDHB* (OMIM 185470), *SDHC* (OMIM 602413), *SDHD* (OMIM 602690), *SMAD4* (OMIM 600993), *STK11* (OMIM 602690), *TP53* (OMIM 191170), *TSC1* (OMIM 605284), *TSC2* (OMIM 191092), *VHL* (OMIM 608537), and *WT1* (OMIM 607102). We also included genes related to cancer phenotypes determined by field experts in the eMERGE network from genes selected by participant sites. These genes were *ATM* (OMIM 607585), *BLM* (OMIM 604610), *CHEK2* (OMIM 604373), *PALB2* (OMIM 610355), *POLD1* (OMIM 174761), and *POLE* (OMIM 174762). Clinical genetic testing for patients in the HCR was performed by commercial Clinical Laboratory Improvement Amendments (CLIA)- and College of American Pathologists (CAP)-accredited molecular diagnostic laboratories. Results from CLIA- and CAP-accredited laboratories were considered highly accurate.[26] Germline variant data in UKB were obtained by whole-exome sequencing data through the UKB data center as described elsewhere.[27]

Variant classification in eMERGEseq was performed by 2 CLIA- and CAP-accredited laboratories according to ACMG and Association for Medical Pathology guidelines with modifications by experts as previously described.[19] Variant classification in the HCR was performed by commercial CLIA- and CAP-accredited molecular genetic testing laboratories.[26] Variant classification in the UKB was performed according to the ACMG and ClinGen guidelines.[19] With the exception of *APC*I1307K, which was classified as a risk allele, all detected variants were classified into pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign. We compared results of shared variants and made the classifications identical across all studies according to the aforementioned guidelines. Details are described in eMethods in the Supplement.

For each gene, we defined patients with pathogenic and likely pathogenic variants as carriers and patients with no rare variants or only benign or likely benign variants as noncarriers, and patients with variants of uncertain significance as carriers of these variants. Only genes with at least 10 carriers in all cohorts combined were included. For *MUTYH,* only biallelic variant carriers were considered. The frequency of carriers in each cohort was consistent with that in previous studies with similar settings.[28-36]

PheWAS Phenotypes

In the eMERGEseq and HCR cohorts, we extracted the *ICD-9-CM* and *ICD-10-CM* data from linked EHRs. The validity of this EHR-based PheWAS approach has been demonstrated in previous studies.[35,37-43] In the UKB, we extracted *ICD-9* and *ICD-10* data from the harmonized health outcome data derived from cancer and death registries, inpatient medical records, and self-reported health outcomes.[23] Details on the clinical data linkage and standardized questionnaires and interviews have been described previously.[23] Specifically, self-reported cancer diagnoses were validated against data from cancer registries and mapped to *ICD-10* codes. Noncancer self-reported health outcomes were also mapped to *ICD-10* codes if applicable. Dates of first occurrence of diseases were also extracted. We mapped all *ICD* codes to phecodes to define the phenotypes for the PheWAS.[17,18,44] Details are provided in eMethods in the Supplement. A total of 3483 unique phecodes were derived from the eMERGEseq data set; 2853, from the HCR data set; and 2693, from the UKB data set. These phecodes covered 15 categories of diseases and conditions, including congenital, cardiovascular, dermatologic, developmental, digestive, endocrine, hematopoietic, infectious, neoplastic, pregnant, psychiatric, pulmonary, genitourinary, musculoskeletal, and symptoms and/or signs.

Statistical Analysis

Statistical analysis was conducted from April 2020 to October 2021. We performed gene-level association tests by collapsing pathogenic and likely pathogenic variants in the same gene. We removed participants with variants of uncertain significance in the same gene from analyses. Each gene-phenotype association was tested independently using the Firth logistic regression.[45,46] In the eMERGEseq cohort, we adjusted for age, EHR length in years, sites, the first 4 principal components, and sex if applicable. In the HCR cohort, we adjusted for age, EHR length in years, self-reported race, and sex if applicable. In the UKB cohort, we adjusted for age, length of follow-up in years, sites, the first 16 principal components suggested by Privé et al,[47] and sex if applicable. The race variable (defined by principal components or self-reported) was included to account for population stratifications. Analyses were performed assuming an autosomal dominant inheritance for all genes except *MUTYH*, for which an autosomal recessive inheritance was assumed, according to their inheritance patterns as hereditary cancer genes documented in the OMIM database,[15] the comprehensive, authoritative collection of gene-phenotype correlations. The association of monoallelic *MUTYH* variants with cancer remains inconclusive[48]; therefore, we did not perform analyses for these carriers. All populations were included. The number of phenotypes evaluated in each cohort is presented in eFigure 1 in the Supplement. We only considered associations found in at least 2 of the 3 studies with the same direction of effect. Meta-analyses were performed assuming a fixed-effect model. We defined 2.5×10^{-5} as the empirical phenome-wide significance threshold at a significance level of $\alpha = .05$ through permutations (eFigure 2 and eMethods in the Supplement). All statistical analyses were performed using R, version 4.0.1 (R Project for Statistical Computing). Figure 2 was produced by the R package gganatogram,[49] which uses the tissue coordinates from the Expression Atlas.[50]

We categorized all gene associations into 3 groups: known or primary associations as documented in the OMIM database, associations related to known phenotypes (eg, elevated cancer antigen 125 for *BRCA1/2*), and potentially new associations. We considered that a known phenotype-gene association was replicated in our analysis if the PheWAS had a $P < .05$ with the expected direction of the effect. Details are described in eMethods in the Supplement.

Sensitivity Analysis

We conducted several sensitivity analyses to test the robustness of the new associations. First, we tested associations lim-

Table 1. Number of Carriers and Noncarriers in the eMERGEseq, HCR, and UKB Cohorts

	eMERGEseq cohort (n = 23 544)			HCR cohort (n = 3242)			UKB cohort (n = 187 234)		
Gene	No. of carriers	No. of noncarriers	Carriers, %	No. of carriers	No. of noncarriers	Carriers, %	No. of carriers	No. of noncarriers	Carriers, %
APC	14	21 903	0.06	22	1931	1.09	28	175 664	0.01
ATM	82	21 863	0.34	29	2309	1.18	1189	153 496	0.64
BRCA1	82	23 012	0.34	92	2705	3.25	211	182 128	0.11
BRCA2	138	22 325	0.58	91	2658	3.22	609	178 147	0.33
CHEK2	272	22 697	1.10	45	2393	1.81	1721	179 702	0.92
MEN1	2	23 269	0.01	10	637	1.53	7	183 949	0.004
MLH1	14	23 214	0.06	15	2371	0.62	78	180 268	0.04
MSH2	16	22 361	0.06	24	2347	0.99	249	177 007	0.13
MSH6	50	22 634	0.21	16	2346	0.67	202	177 955	0.11
MUTYH (biallelic)	4	22 436	0.02	3	2113	0.14	29	182 552	0.02
PALB2	28	22 925	0.13	30	2391	1.22	367	181 218	0.20
PMS2	54	22 300	0.23	17	2326	0.71	283	185 524	0.15
PTEN	13	23 184	0.06	3	2518	0.12	26	183 442	0.01
RB1	2	23 105	0.01	6	280	2.08	8	174 527	0.004
RET	34	22 745	0.14	10	370	2.58	35	176 515	0.02
SDHB	6	23 397	0.02	4	659	0.60	22	183 041	0.01
SDHC	6	23 340	0.02	0	704	0	27	179 271	0.01
SDHD	4	23 435	0.02	5	653	0.76	21	185 466	0.01
TP53	12	23 336	0.06	4	2557	0.15	28	183 238	0.01
TSC1	5	22 792	0.02	0	690	0	33	174 326	0.02
TSC2	12	21 598	0.05	0	680	0	23	183 078	0.01
VHL	5	23 329	0.02	8	872	0.90	16	184 649	0.01
WT1	3	23 215	0.01	0	241	0	11	186 298	0.01

Abbreviations: eMERGEseq, Electronic Medical Records and Genomics Sequencing; HCR, hereditary cancer registry; UKB, UK Biobank.

iting the individuals to those with European ancestry. For the eMERGEseq and UKB cohorts, we also derived ancestral specific principal components from genetic data as additional covariates. Second, to investigate whether associations with noncancer phenotypes were associated with prior cancer diagnoses, we restricted analyses to those without any cancer diagnoses (excluding basal cell carcinomas) before enrollment. We used the UKB data set because dates of cancer diagnoses were ascertained through cancer registries. Second, to investigate whether the observed associations between *CHEK2* and hematological malignant neoplasms were associated with prior cancer diagnoses, we restricted analyses to those without cancer diagnoses before blood sampling in the UKB data set. In addition, we conducted another analysis by removing participants with any cancer diagnosis within 3 years after blood sampling. Third, to investigate whether the observed *CHEK*2 and leukemia association differed by subtypes, we evaluated associations of *CHEK2* with subtypes of leukemia. Finally, we compared association results of *BRCA1* with *BRCA2* found in this PheWAS.

EHR Reviews

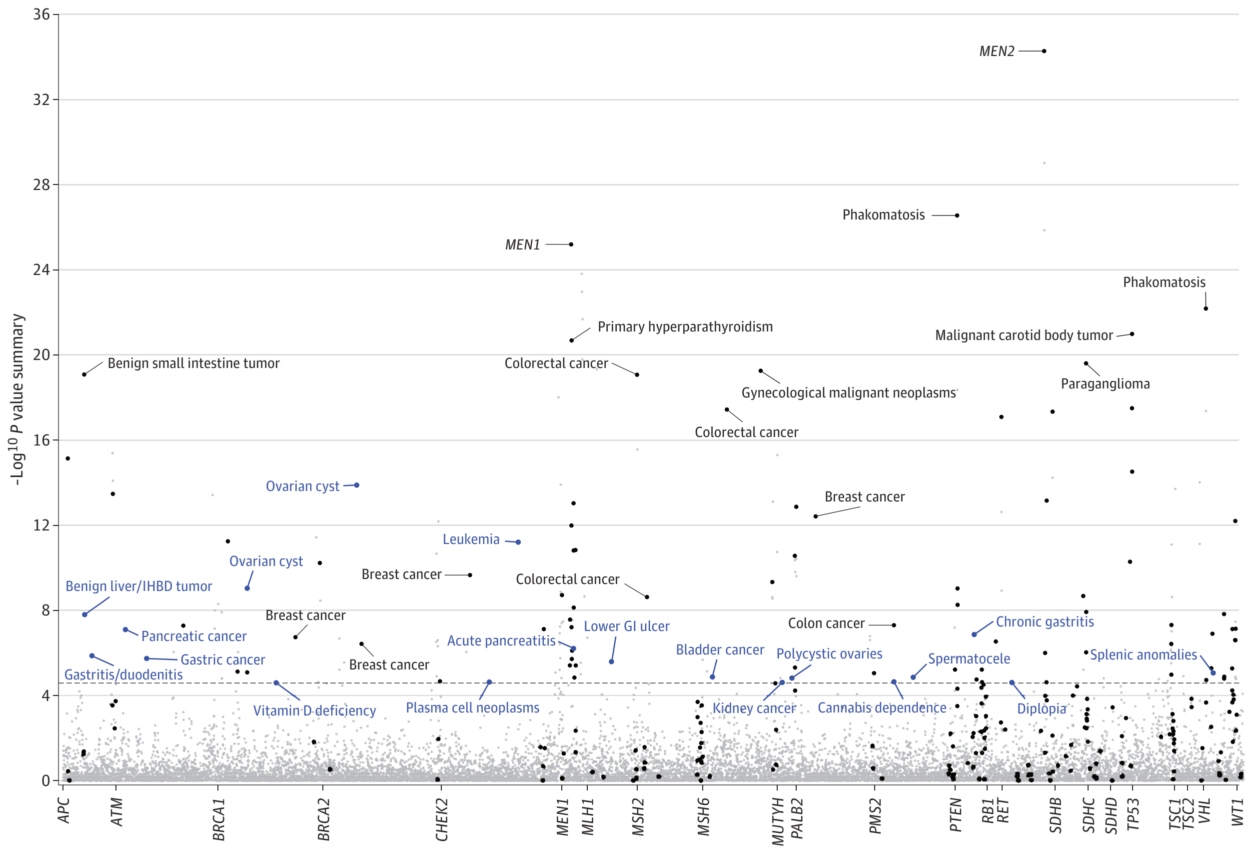
We conducted EHR reviews for participants with readily accessible EHRs at Vanderbilt University Medical Center to gather more information about diagnoses related to new associations. We verified diagnoses by reviewing pathology reports, radiology imaging results, and clinical narratives.

Results

We included 214 020 participants from the 3 cohorts. Baseline demographic characteristics and the follow-up time for each cohort are summarized in eTable 2 in the Supplement. Participants in the eMERGEseq cohort (n = 23 544) had a mean (SD) age of 47.8 (23.7) years with a mean (SD) follow-up of 12.7 (7.4) years; 5145 (21.9%) had non-European ancestry, 12 611 (53.6%) were women, and 10 933 (46.4%) were men. The HCR cohort (n = 3242) had a mean (SD) age of 52.5 (15.5) years with a mean (SD) follow-up of 8.8 (6.5) years; 413 (12.7%) had non-European ancestry, 2851 (87.9%) were women, and 391 (12.1%) were men. The UKB cohort (n = 187 234) had a mean (SD) age at recruitment of 56.7 (8.1) years with a mean (SD) follow-up time of 12.4 (1.0) years; 11 293 (6.0%) had non-European ancestry; 104 055 (55.6%) were women and 83 179 (44.4%) were men. The distribution of carriers for each gene is summarized in **Table 1**. A total of 858 carriers were identified in the eMERGEseq cohort; 434, in the HCR cohort; and 5223 in the UKB cohort. The distribution of carriers for each gene by ancestral group is summarized in eTable 3 in the Supplement.

We first assessed whether the PheWAS could replicate known gene-phenotype associations. Our PheWAS replicated 38 of 38 primary gene-cancer associations (100%) and 164 of 235 gene-phenotype associations (69.8%) documented in OMIM, which reports diseases and symptoms as-

Figure 1. Phenome-Wide Association Study to Confirm Known Gene-Phenotype Associations and Uncover New Associations for Hereditary Cancer Genes



Meta-analysis results of phenome-wide association study in the Electronic Medical Records and Genomics Sequencing, Hereditary Cancer Registry, and UK Biobank data sets are shown. Strength of the association is plotted along the y-axis as $-\log^{10} P$ value summary, and phenotypes are represented on the x-axis, grouped by each gene. Black dots represent the known associated phenotypes. Labeled phenotypes with blue dots represent new gene-phenotype associations. The dashed line indicates $P = 2.5 \times 10^{-5}$, representing the empirical phenome-wide significance. GI indicates gastrointestinal tract; IHBD, intrahepatic bile duct; *MEN1*, multiple endocrine neoplasia syndrome type 1; and *MEN2*, multiple endocrine neoplasia syndrome type 2.

sociated with the genes (**Figure 1** and eTable 4 in the Supplement). The probability of replicating associations in at least 164 of 235 tests by chance, under the null hypothesis of no association, is $P = 2.13 \times 10^{-154}$.

A total of 193 gene-phenotype associations exceeded the phenome-wide significance ($P < 2.5 \times 10^{-5}$). After removing known associations, 19 new associations that have not been documented in the OMIM database were found in 13 hereditary cancer genes (**Table 2** and **Figure 2**). These consisted of 6 associations with malignant tumors, including *CHEK2* with leukemia (odds ratio [OR], 3.81 [95% CI, 2.64-5.48]) and plasma cell neoplasms (OR, 3.12 [95% CI, 1.84-5.28]), *ATM* with gastric cancer (OR, 4.27 [95% CI, 2.35-7.44]) and pancreatic cancer (OR, 4.44 [95% CI, 2.66-7.40]), *MUTYH* (biallelic) with kidney cancer (OR, 32.28 [95% CI, 6.40-162.73]), *MSH6* with bladder cancer (OR, 5.63 [95% CI, 2.75-11.49]), and an association of *APC* with benign liver/intrahepatic bile duct tumors (OR, 52.01 [95% CI, 14.29-189.29]). Ten genes were associated with nonneoplastic diseases (eg, *BRCA1* [OR, 3.15 (95% CI, 2.22-4.46)] and *BRCA2* [OR, 3.12 (95% CI, 2.36-4.12)] with ovarian cysts, *MEN1* with acute pancreatitis [OR, 33.45 (95% CI, 9.25-121.02)], *APC* with gastritis and duodenitis [OR, 4.66 (95% CI, 2.61-8.33)], and *PTEN* with chronic gastritis [OR, 15.68 (95% CI, 6.01-40.92)]).

All results of the sensitivity analyses were consistent with the main findings. Results of new associations remained largely unchanged in the analyses conducted in European descendants only (eTable 5 in the Supplement). After removing participants with prior cancer diagnoses, associations between *BRCA1/2* and ovarian cyst, *PTEN* and chronic gastritis, and *MEN1* with acute pancreatitis remained statistically significant (eTable 6 in the Supplement). For associations of *CHEK2* with hematological cancers, removing participants with prior cancer diagnoses or even those with cancer diagnoses within 3 years after blood draw did not substantially change the associations (eTable 7 in the Supplement). No substantial differences were detected in the associations of *CHEK2* with subtypes of leukemia (eTable 8 in the Supplement). No substantial differences in phenotypic associations between *BRCA1* and *BRCA2* were found (eTable 9 in the Supplement).

Table 2. New Associations Discovered via PheWAS[a]

Gene	Phenotype	Cohort, OR (95% CI) eMERGEseq	HCR	UKB	Meta-analysis	*P* value Summary	Het
Neoplastic diseases							
ATM	Pancreatic cancer	2.54 (0.39-16.39)	3.68 (0.77-17.52)	4.79 (2.72-8.43)	4.44 (2.66-7.40)	7.88×10^{-8}	.79
ATM	Gastric cancer	4.62 (0.61-34.79)	NA	4.24 (2.27-7.90)	4.27 (2.35-7.74)	1.80×10^{-6}	.94
CHEK2	Leukemia	4.42 (2.18-8.94)	5.04 (1.00-25.41)	3.52 (2.26-5.47)	3.81 (2.64-5.48)	6.18×10^{-12}	.81
CHEK2	Plasma cell neoplasms[b]	2.66 (0.90-7.90)	NA	3.28 (1.79-5.98)	3.12 (1.84-5.28)	2.30×10^{-5}	.74
MSH6	Bladder cancer	8.30 (2.33-29.54)	18.98 (4.32-83.30)	2.28 (0.79-6.61)	5.63 (2.75-11.49)	1.33×10^{-5}	.06
MUTYH	Kidney cancer	NA	84.13 (8.47-836.11)	12.57 (1.29-122.74)	32.28 (6.40-162.73)	2.50×10^{-5}	.25
APC	Benign liver/IHBD tumor	61.01 (7.66-485.98)	26.47 (3.48-201.34)	146.80 (16.10-586.83)	52.01 (14.29-189.29)	1.57×10^{-8}	.62
Nonneoplastic diseases							
APC	Gastritis and duodenitis	3.32 (0.98-11.25)	9.43 (3.66-24.31)	2.91 (1.16-7.29)	4.66 (2.61-8.33)	1.34×10^{-6}	.18
BRCA1	Ovarian cyst	5.91 (3.40-10.29)	1.80 (1.05-3.07)	2.94 (1.30-6.64)	3.15 (2.22-4.46)	9.09×10^{-10}	.01
BRCA1	Vitamin D deficiency	0.51 (0.28-0.93)	0.17 (0.08-0.38)	0.57 (0.34-0.97)	0.43 (0.30-0.62)	2.50×10^{-5}	.04
BRCA2	Ovarian cyst	4.07 (2.56-6.48)	2.64 (1.56-4.46)	2.72 (1.71-4.33)	3.12 (2.36-4.12)	1.29×10^{-14}	.37
MEN1	Acute pancreatitis	48.47 (3.07-765.51)	27.26 (4.68-158.68)	37.49 (2.86-490.91)	33.45 (9.25-121.02)	6.09×10^{-7}	.94
PTEN	Chronic gastritis	3.84 (0.51-28.68)	15.93 (1.30-194.97)	26.06 (7.75-87.58)	15.68 (6.01-40.92)	1.35×10^{-7}	.28
MUTYH	Polycystic ovaries	33.94 (2.30-501.28)	53.76 (5.76-502.08)	NA	44.57 (7.99-248.73)	1.50×10^{-5}	.80
MLH1	Lower GI ulcer	26.8 (5.15-139.47)	12.39 (1.98-77.46)	NA	18.97 (5.57-64.67)	2.50×10^{-5}	.54
PMS2	Spermatocele	20.48 (4.14-101.22)	19.13 (1.51-242.84)	NA	20.09 (5.19-77.7)	1.38×10^{-5}	.96
PMS2	Cannabis dependence	15.68 (2.57-95.76)	184.31 (12.71-2491.54)	NA	29.34 (6.15-139.97)	2.24×10^{-5}	.18
RET	Diplopia	9.90 (3.04-32.23)	7.99 (0.82-77.72)	NA	9.46 (3.32-26.97)	2.49×10^{-5}	.87
VHL	Splenic anomalies	111.40 (6.60-1880.13)	131.16 (4.97-3463.79)	NA	119.45 (14.07-1014.39)	1.17×10^{-5}	.94

Abbreviations: eMERGEseq, Electronic Medical Records and Genomics Sequencing; GI, gastrointestinal tract; HCR, Hereditary Cancer Registry; IHBD, intrahepatic bile duct; NA, not applicable; OR, odds ratio; PheWAS, phenome-wide association study; UKB, UK Biobank.

[a] We used Firth logistic regression in this PheWAS assuming a dominant model except for *MUTYH*, which assumed a recessive model. Owing to the scarceness of carriers of *VHL* and *APC* and a low prevalence of cannabis use in the HCR cohort, wide CIs were observed, and caution should be exercised when interpreting these results. NA indicates no phenotype was found among carriers for the gene in the cohort, and thus we were not able to evaluate the association. Results with a $P < 2.5 \times 10^{-5}$ with a consistent direction of effect in at least 2 cohorts are included.

[b] Plasma cell neoplasms also include multiple myeloma.

By reviewing EHRs of participants in the HCR cohort, we verified the diagnosis of renal cell carcinoma in the biallelic *MUTYH* variant carrier, which was consistent with the diagnosis of this cancer in the biallelic *MUTYH* variant carrier in the UKB cohort. We found a diagnosis of thyroid cancer in the *RET* carrier with diplopia. We also found that 7 of 20 *BRCA1* carriers with ovarian cysts were diagnosed with ovarian cancer, whereas only 2 such diagnoses were found in *BRCA2* carriers with ovarian cysts (2 of 24). However, the difference between *BRCA1* and *BRCA2* was not statistically significant ($P = .06$). We also did not find evidence that patients who were *BRCA1/2* carriers with ovarian cysts were actually cases of ovarian cancer that had been missed. We did not find pancreatic cancer diagnoses among *MEN1* carriers with acute pancreatitis.

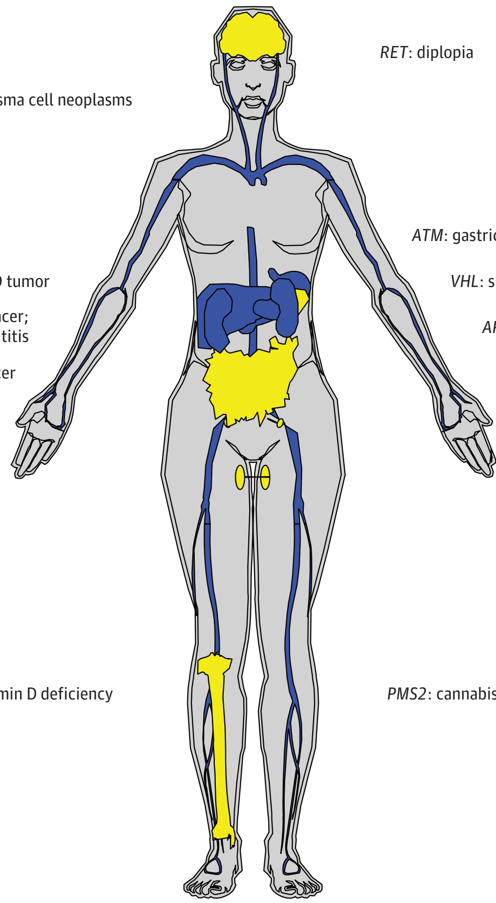
Discussion

In this study, we demonstrate the feasibility of rapid phenotype discovery by the PheWAS approach by replicating most known associations documented in the OMIM that represented knowledge accumulated in decades. We identified 19 new gene-phenotype associations, which spanned categories of diseases, including the neoplastic, genitourinary, digestive, congenital, metabolic, psychiatric, and neurological categories, supporting our hypothesis that hereditary cancer syndromes are associated with multiple diseases.

This study revealed a novel gene-cancer association between biallelic *MUTYH* variants and kidney cancer. Although monogenic germline *MUTYH* pathogenic variants have been identified in patients with renal cell carcinoma,[51] previous studies[11,48] that used data from high-risk families and probands reported no occurrence of this cancer among biallelic *MUTYH* variant carriers but did report benign kidney lesions. Although few studies have investigated the role of *MUTYH* in kidney cancers, some mutation signatures of genomic instability have been found to be more common in these tumors than other solid tumors.[52] Further molecular studies are needed to illuminate the observed association.

This study provides additional evidence for associations of cancers that have not been documented in the OMIM data-

Figure 2. New Gene-Phenotype Associations Uncovered by Phenome-Wide Association Study, Organized by Organs



Organs labeled blue represent neoplastic sites; organs labeled yellow represent nonneoplastic sites. GI indicates gastrointestinal tract, IHBD, intrahepatic bile duct.

base but were reported in previous literature, including *ATM* with gastric and pancreatic cancer,[53,54] *MSH6* with bladder cancer,[55] and *CHEK2* with leukemia.[56-58] Notably, a recent study[59] suggested that loss of *CHEK2* function increased the risk of clonal hematopoiesis of indeterminate potential, which was a risk factor for hematological malignant neoplasms.[60] Furthermore, it was found that prior cancer therapies could increase the risk of clonal hematopoiesis of indeterminate potential.[61] We observed that associations with leukemia or multiple myeloma persisted after removing participants with cancer diagnosed before and within 3 years of blood sampling. Nonetheless, we could not fully exclude the possibility that somatic variants of *CHEK2* detected owing to clonal expansions contribute to the observed association. Future studies that include additional types of tissues can help exclude the somatic variants and validate the observed associations.

This study also revealed new noncancer associations that would have been difficult to detect in studies focusing on cancers or using prior knowledge.[62] These phenotypes included inflammation-related disorders, which were consistent with previous findings.[63,64] For example, a recent study[63] identified an essential role of *MEN1* in exocrine pancreas homeostasis in response to inflammation that contributes to pancreatitis in mouse models. A previous study[65] suggested that *MUTYH* contributed to inflammatory-related disorders. We found that homozygous or compound heterozygous *MUTYH* carriers had an association with polycystic ovaries, for which chronic inflammation has been proposed to be a key contributor.[66] We also found a Beçhet syndrome diagnosis in a *MUTYH* biallelic variant carrier in this study. Taken together, these findings provide supporting evidence for a role of *MUTYH* in inflammatory-related disorders.

Results of EHR review suggested that some of the noncancer phenotypes could be symptoms of underlying diseases that had been known. For example, the association of *RET* with diplopia was likely to be mediated by neuroendocrine disorders, including tumors. However, diplopia has been largely underreported in patients with multiple endocrine neoplasia type 2 in previous studies and thus has not been documented in the OMIM database. We believe that recognizing such relevant symptoms can be important for the management of multiple endocrine neoplasia type 2. Identification of symptoms such as these may also serve an early sign of underlying diseases such as cancers and thus facilitate early detection, as shown in previous studies.[67,68]

Owing to the small number of carriers identified for genes including *MUTYH*, *VHL*, and *APC*, additional studies are needed to validate the new associations identified in this study. A previous study[69] suggested that *BRCA1/2* could have a different role in diseases. However, we did not observe different associations in our PheWAS. Follow-up studies are needed to test this hypothesis.

Limitations

Limitations of this study include a relatively small sample size of populations of non-European descendants. This could potentially limit the generalizability of our findings to these populations, although we included them in analyses. We anticipate that large EHR-based cohorts including more diverse populations, such as the *All of Us* research program,[70] will identify additional phenotypes associated with these genes and increase the generalizability of the findings to these understudied populations.

Conclusions

In this PheWAS of 3 cohorts using data derived from the EHRs of 214 020 participants, we studied a wide range of phenotypes associated with hereditary cancer genes. We identified 19 new gene-phenotype associations, including both neoplastic and nonneoplastic diseases. These findings suggest that PheWAS in EHR data sets has the potential to expand our knowledge of the phenotypes and disease processes in patients with pathogenic and likely pathogenic variants in hereditary cancer genes. New clinical management protocols could be developed based on these findings, so future research replicating these new associations will be important. Large EHR-based cohorts of diverse populations will help reveal the true clinical spectrum of genetic diseases, aid in variant interpretation, and ultimately facilitate precision medicine for all patients.

ARTICLE INFORMATION

Accepted for Publication: January 7, 2022.

Published Online: April 21, 2022. doi:10.1001/jamaoncol.2022.0373

Author Affiliations: National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland (Zeng, Denny); Center for Precision Medicine, Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee (Bastarache, Bland, Peterson, Roden); Department of Biostatistics, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, Tennessee (Tao); Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas (Venner, Gibbs); Center for Human Genetics, Marshfield Clinic Research Institute, Marshfield, Wisconsin (Hebbring); Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Andujar, Wiesner); Clinical and Translational Hereditary Cancer Program, Division of Genetic Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee (Andujar, Wiesner); Department of Biomedical Informatics and Medical Education, University of Washington School of Medicine, Seattle (Crosslin); School of Graduate Studies and Research, Meharry Medical College, Nashville, Tennessee (Pratap); Department of Microbiology, Immunology and Physiology, Meharry Medical College, Nashville, Tennessee (Cooley); Center for Genetic Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Pacheco); PRecisiOn Medicine Translational Research (PROMoTeR) Center, Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Christensen); Department of Population Medicine, Harvard Medical School, Boston, Massachusetts (Christensen); Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Perez, Zawatsky); Centre Universitaire de Santé McGill, McGill University Health Centre, Montreal, Quebec, Canada (Witkowski); Laboratory for Molecular Medicine, Partners Healthcare Personalized Medicine, Cambridge, Massachusetts (Zouk); Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston (Zouk); Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, New York (Weng); Genetic Services and Kaiser Permanente Washington Health Research Institute, Kaiser Permanente of Washington, Seattle (Leppig); Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (Sleiman, Hakonarson); Division of Human Genetics, Department of Pediatrics, The University of Pennsylvania Perelman School of Medicine, Philadelphia (Sleiman, Hakonarson); Genomic Medicine Institute, Geisinger, Danville, Pennsylvania (Williams); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Luo); Department of Medicine (Medical Genetics), University of Washington, Seattle (Jarvik); Department of Genome Sciences, University of Washington, Seattle (Jarvik); Brigham and Women's Hospital, Broad Institute, Ariadne Labs and Harvard Medical School, Boston, Massachusetts (Green); Department of Pediatrics, Columbia University, New York, New York (Chung); Department of Medicine, Columbia University, New York, New York (Chung); Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, New York (Gharavi); Center for Precision Medicine and Genomics, Department of Medicine, Columbia University Irving Medical Center, New York, New York (Gharavi); Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Lennon); Medical & Population Genetics Program and Genomics Platform, Broad Institute of MIT and Harvard Cambridge, Cambridge, Massachusetts (Rehm); Center for Genomic Medicine, Massachusetts General Hospital, Boston (Rehm); Department of Pathology, Harvard Medical School, Boston, Massachusetts (Rehm); Divisions of Cardiovascular Medicine and Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Roden); Department of Pharmacology, Vanderbilt University, Nashville, Tennessee (Roden)
.

Author Contributions: Drs Zeng and Denny had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Zeng, Leppig, Williams, Jarvik, Green, Roden, Wiesner, Denny.
Acquisition, analysis, or interpretation of data: Zeng, Bastarache, Tao, Venner, Hebbring, Andujar, Bland, Crosslin, Pratap, Cooley, Pacheco, Christensen, Perez, Blout Zawatsky, Witkowski, Zouk, Weng, Sleiman, Hakonarson, Williams, Luo, Jarvik, Chung, Gharavi, Lennon, Rehm, Gibbs, Peterson, Roden, Wiesner, Denny.
Drafting of the manuscript: Zeng, Bland, Crosslin, Jarvik, Wiesner.
Critical revision of the manuscript for important intellectual content: Zeng, Bastarache, Tao, Venner, Hebbring, Andujar, Pratap, Cooley, Pacheco, Christensen, Perez, Blout Zawatsky, Witkowski, Zouk, Weng, Leppig, Sleiman, Hakonarson, Williams, Luo, Jarvik, Green, Chung, Gharavi, Lennon, Rehm, Gibbs, Peterson, Roden, Wiesner, Denny.
Statistical analysis: Zeng, Bastarache, Tao, Andujar, Sleiman.
Obtained funding: Hebbring, Crosslin, Pratap, Williams, Jarvik, Chung, Rehm, Roden, Denny.
Administrative, technical, or material support: Venner, Bland, Christensen, Perez, Blout Zawatsky, Zouk, Weng, Hakonarson, Luo, Jarvik, Gibbs, Peterson, Wiesner, Denny.
Supervision: Bastarache, Pratap, Hakonarson, Jarvik, Peterson, Denny.

Conflict of Interest Disclosures: Ms Bastarache reported receiving royalties from Nashville Biotech and consulting for Galatea Bio Inc outside the submitted work. Dr Hebbring reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study. Ms Bland reported receiving grants from the National Human Genomic Research Institute of the NIH (NHGRI) during the conduct of the study. Dr Crosslin reported receiving grants from the NHGRI during the conduct of the study and personal fees from UnitedHealth Group outside the submitted work. Dr Christensen reported receiving grants from Sanford Health and the NIH outside the submitted work. Dr Zouk reported receiving grants from the NHGRI during the conduct of the study. Dr Williams reported receiving grants from NIH during the conduct of the study. Dr Luo reported receiving grants from the NIH during the conduct of the study. Dr Jarvik reported receiving grants from the NHGRI during the conduct of the study. Dr Green reported receiving personal fees from Genomic Life, VinBigData, Meenta, PlumCare, OptumLabs, GRAIL, Embrome, Allelica, GenomeWeb LLC, AIA, and Verily Life Sciences outside the submitted work. Dr Gharavi reported receiving grants from the Renal Research Institute and Natera Inc, serving on the advisory boards of Novartis International AG and Travere Therapeutics, conference participation for Sanofi SA, and consulting for Goldfinch Bio Inc. Dr Rehm reported receiving grants from the NIH during the conduct of the study. Dr Peterson reported receiving grants from NHGRI during the conduct of the study. Dr Wiesner reported grants from NHGRI and being a professor for Vanderbilt Ingram Cancer Center Ingram Cancer Research during the conduct of the study. Dr Denny reported receiving royalties from Vanderbilt University Medical Center–licensed use phenome-wide association study technology on Vanderbilt's DNA biobank to Nashville Biosciences. No other disclosures were reported.

Funding/Support: This study was supported by grant R01LM010685 from the National Library of Medicine and funding to the eMERGE sites through the following: grants U01HG8657, U01HG006375, and U01HG004610 (Kaiser Permanente Washington/University of Washington); U01HG8685 (Brigham and Women's Hospital); U01HG8672, U01HG006378, and U01HG004608 (Vanderbilt University Medical Center); U01HG8666 and U01HG006828 (Cincinnati Children's Hospital Medical Center); U01HG6379 and U01HG04599 (Mayo Clinic); U01HG8679 and U01HG006382 (Geisinger Clinic); U01HG008680 (Columbia University Health Sciences); U01HG8684 and U01HG006830 (Children's Hospital of Philadelphia); U01HG8673, U01HG006388, and U01HG004609 (Northwestern University); U54MD007593 and U54MD007586 (Meharry Medical College); U01HG8676 (Partners Healthcare/Broad Institute); U01HG8664 (Baylor College of Medicine); U01HG006389 (Essentia Institute of Rural Health, Marshfield Clinic Research Foundation and Pennsylvania State University); U01HG006380 (Icahn School of Medicine at Mount Sinai); U01HG8701, U01HG006385, and U01HG04603 (Vanderbilt University Medical Center serving as the Coordinating Center) from the NHGRI; funding to eMERGE genotyping centers through grants U01HG004438 (CIDR) and U01HG004424 (the Broad Institute); funding for Vanderbilt University Medical Center's Synthetic Derivative, Research Derivative, and BioVU by institutional funding and Clinical and Translational Science Awards grant ULTR000445 from National Center for Advancing Translational Sciences/NIH; by grant HG200417-01 from the Intramural Research Program of the NHGRI; by funds from the Vanderbilt-Ingram Cancer Center Ingram Professorship program (Dr Wiesner); and by grant HG200417 from the Intramural Research Program of the National Human Genome Research Institute (Drs Zeng and Denny since joining the NIH).

Role of the Funders/Sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Jacob Keaton, PhD, and Tracey Ferrara, PhD, NHGRI, NIH, provided logistical support. Jeremy Warner, MD, MS, Vanderbilt University Medical Center, Thomas Cassini, MD, NHGRI, NIH, and Huan Mo, MD, MD Anderson Cancer Center, provided critical comments. These individuals did not receive any compensation for this work.

Additional Information: Much of the work by Drs Zeng and Denny on this project was performed at Vanderbilt University before joining the NIH.

REFERENCES

1. Delude CM. Deep phenotyping: the details of disease. *Nature*. 2015;527(7576):S14-S15. doi:10.1038/527S14a

2. Claussnitzer M, Cho JH, Collins R, et al. A brief history of human disease genetics. *Nature*. 2020;577(7789):179-189. doi:10.1038/s41586-019-1879-7

3. Bellacosa A. Developmental disease and cancer: biological and clinical overlaps. *Am J Med Genet A*. 2013;161A(11):2788-2796. doi:10.1002/ajmg.a.36267

4. Morton SU, Shimamura A, Newburger PE, et al. Association of damaging variants in genes with increased cancer risk among patients with congenital heart disease. *JAMA Cardiol*. 2021;6(4):457-462. doi:10.1001/jamacardio.2020.4947

5. Yehia L, Keel E, Eng C. The clinical spectrum of *PTEN* mutations. *Annu Rev Med*. 2020;71:103-116. doi:10.1146/annurev-med-052218-125823

6. Pinna V, Daniele P, Calcagni G, et al. Prevalence, type, and molecular spectrum of *NF1* mutations in patients with neurofibromatosis type 1 and congenital heart disease. *Genes (Basel)*. 2019;10(9):E675. doi:10.3390/genes10090675

7. Chong JX, Buckingham KJ, Jhangiani SN, et al; Centers for Mendelian Genomics. The genetic basis of mendelian phenotypes: discoveries, challenges, and opportunities. *Am J Hum Genet*. 2015;97(2):199-215. doi:10.1016/j.ajhg.2015.06.009

8. Deans AR, Lewis SE, Huala E, et al. Finding our way through phenotypes. *PLoS Biol*. 2015;13(1):e1002033. doi:10.1371/journal.pbio.1002033

9. Gayther SA, Warren W, Mazoyer S, et al. Germline mutations of the *BRCA1* gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. *Nat Genet*. 1995;11(4):428-433. doi:10.1038/ng1295-428

10. Weren RD, Ligtenberg MJ, Kets CM, et al. A germline homozygous mutation in the base-excision repair gene *NTHL1* causes adenomatous polyposis and colorectal cancer. *Nat Genet*. 2015;47(6):668-671. doi:10.1038/ng.3287

11. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology*. 2009;137(6):1976-85.e1, 10. doi:10.1053/j.gastro.2009.08.052

12. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of *APC* and *MUTYH* mutations in patients with multiple colorectal adenomas. *JAMA*. 2012;308(5):485-492. doi:10.1001/jama.2012.8780

13. Kuchenbaecker KB, Hopper JL, Barnes DR, et al; BRCA1 and BRCA2 Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *JAMA*. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

14. Au KS, Williams AT, Roach ES, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med*. 2007;9(2):88-100. doi:10.1097/GIM.0b013e31803068c7

15. Amberger JS, Bocchini CA, Scott AF, Hamosh A. OMIM.org: leveraging knowledge across phenotype-gene relationships. *Nucleic Acids Res*. 2019;47(D1):D1038-D1043. doi:10.1093/nar/gky1151

16. Rath A, Olry A, Dhombres F, Brandt MM, Urbero B, Ayme S. Representation of rare diseases in health information systems: the Orphanet approach to serve a wide range of end users. *Hum Mutat*. 2012;33(5):803-808. doi:10.1002/humu.22078

17. Denny JC, Bastarache L, Ritchie MD, et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol*. 2013;31(12):1102-1110. doi:10.1038/nbt.2749

18. Zhou W, Nielsen JB, Fritsche LG, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet*. 2018;50(9):1335-1341. doi:10.1038/s41588-018-0184-y

19. eMERGE Consortium. Harmonizing clinical sequencing and interpretation for the eMERGE III Network. *Am J Hum Genet*. 2019;105(3):588-605. doi:10.1016/j.ajhg.2019.07.018

20. Wiesner GL, Kulchak Rahm A, Appelbaum P, et al. Returning results in the genomic era: initial experiences of the eMERGE Network. *J Pers Med*. 2020;10(2):E30. doi:10.3390/jpm10020030

21. Daly MB, Pal T, Berry MP, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(1):77-102. doi:10.6004/jnccn.2021.0001

22. Danciu I, Cowan JD, Basford M, et al. Secondary use of clinical data: the Vanderbilt approach. *J Biomed Inform*. 2014;52:28-35. doi:10.1016/j.jbi.2014.02.003

23. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203-209. doi:10.1038/s41586-018-0579-z

24. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249-255. doi:10.1038/gim.2016.190

25. Miller DT, Lee K, Chung WK, et al; ACMG Secondary Findings Working Group. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1381-1390. doi:10.1038/s41436-021-01172-3

26. Lincoln SE, Kobayashi Y, Anderson MJ, et al. A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. *J Mol Diagn*. 2015;17(5):533-544. doi:10.1016/j.jmoldx.2015.04.009

27. Wang Q, Dhindsa RS, Carss K, et al; AstraZeneca Genomics Initiative. Rare variant contribution to human disease in 281,104 UK Biobank exomes. *Nature*. 2021;597(7877):527-532. doi:10.1038/s41586-021-03855-y

28. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. 2014;312(18):1870-1879. doi:10.1001/jama.2014.14601

29. Miller DT, Lee K, Chung WK, et al; ACMG Secondary Findings Working Group. Correction to: ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1582-1584. doi:10.1038/s41436-021-01278-8

30. Olfson E, Cottrell CE, Davidson NO, et al. Identification of medically actionable secondary findings in the 1000 genomes. *PLoS One*. 2015;10(9):e0135193. doi:10.1371/journal.pone.0135193

31. Amendola LM, Dorschner MO, Robertson PD, et al. Actionable exomic incidental findings in 6503 participants: challenges of variant classification. *Genome Res*. 2015;25(3):305-315. doi:10.1101/gr.183483.114

32. Schwartz MLB, McCormick CZ, Lazzeri AL, et al. A model for genome-first care: returning secondary genomic findings to participants and their healthcare providers in a large research cohort. *Am J Hum Genet*. 2018;103(3):328-337. doi:10.1016/j.ajhg.2018.07.009

33. Van Hout CV, Tachmazidou I, Backman JD, et al; Geisinger-Regeneron DiscovEHR Collaboration; Regeneron Genetics Center. Exome sequencing and characterization of 49,960 individuals in the UK Biobank. *Nature*. 2020;586(7831):749-756. doi:10.1038/s41586-020-2853-0

34. Grzymski JJ, Elhanan G, Morales Rosado JA, et al. Population genetic screening efficiently identifies carriers of autosomal dominant diseases. *Nat Med*. 2020;26(8):1235-1239. doi:10.1038/s41591-020-0982-5

35. Park J, Lucas AM, Zhang X, et al. Exome-wide evaluation of rare coding variants using electronic health records identifies new gene-phenotype associations. *Nat Med*. 2021;27(1):66-72. doi:10.1038/s41591-020-1133-8

36. Susswein LR, Marshall ML, Nusbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genet Med*. 2016;18(8):823-832. doi:10.1038/gim.2015.166

37. Bastarache L. Using phecodes for research with the electronic health record: from PheWAS to PheRS. *Annu Rev Biomed Data Sci*. 2021;4:1-19. doi:10.1146/annurev-biodatasci-122320-112352

38. Sinnott JA, Cai F, Yu S, et al. PheProb: probabilistic phenotyping using diagnosis codes to improve power for genetic association studies. *J Am Med Inform Assoc*. 2018;25(10):1359-1365. doi:10.1093/jamia/ocy056

39. Ye Z, Mayer J, Ivacic L, et al. Phenome-wide association studies (PheWASs) for functional variants. *Eur J Hum Genet*. 2015;23(4):523-529. doi:10.1038/ejhg.2014.123

40. Liao KP, Sparks JA, Hejblum BP, et al. Phenome-wide association study of autoantibodies to citrullinated and noncitrullinated epitopes in rheumatoid arthritis. *Arthritis Rheumatol*. 2017;69(4):742-749. doi:10.1002/art.39974

41. Wang L, Zhang X, Meng X, et al. Methodology in phenome-wide association studies: a systematic review. *J Med Genet*. 2021;58(11):720-728. doi:10.1136/jmedgenet-2021-107696

42. Bai W, Suzuki H, Huang J, et al. A population-based phenome-wide association study of cardiac and aortic structure and function. *Nat Med*. 2020;26(10):1654-1662. doi:10.1038/s41591-020-1009-y

43. Belbin GM, Cullina S, Wenric S, et al; CBIPM Genomics Team; Regeneron Genetics Center. Toward a fine-scale population health monitoring system. *Cell*. 2021;184(8):2068-2083.e11. doi:10.1016/j.cell.2021.03.034

44. Wu P, Gifford A, Meng X, et al. Mapping *ICD-10* and *ICD-10-CM* codes to phecodes: workflow development and initial evaluation. *JMIR Med Inform*. 2019;7(4):e14325. doi:10.2196/14325

45. Doerken S, Avalos M, Lagarde E, Schumacher M. Penalized logistic regression with low prevalence exposures beyond high dimensional settings. *PLoS One*. 2019;14(5):e0217057. doi:10.1371/journal.pone.0217057

46. Firth D. Bias reduction of maximum-likelihood-estimates. *Biometrika*. 1993;80(1):27-38. doi:10.1093/biomet/80.1.27

47. Privé F, Luu K, Blum MGB, McGrath JJ, Vilhjálmsson BJ. Efficient toolkit implementing best practices for principal component analysis of population genetic data. *Bioinformatics*. 2020;36(16):4449-4457. doi:10.1093/bioinformatics/btaa520

48. Win AK, Reece JC, Dowty JG, et al. Risk of extracolonic cancers for people with biallelic and monoallelic mutations in *MUTYH*. *Int J Cancer*. 2016;139(7):1557-1563. doi:10.1002/ijc.30197

49. Maag JLV. gganatogram: an R package for modular visualisation of anatograms and tissues based on ggplot2 (version 1; referees: 1 approved). *F1000Research*. 2018. doi:10.12688/f1000research.16409.1

50. Expression Atlas: Gene Expression Across Species and Biological Conditions. Accessed March 30, 2022. https://www.ebi.ac.uk/gxa/home

51. Ged Y, Chaim JL, DiNatale RG, et al. DNA damage repair pathway alterations in metastatic clear cell renal cell carcinoma and implications on systemic therapy. *J Immunother Cancer*. 2020;8(1):e000230. doi:10.1136/jitc-2019-000230

52. Alexandrov LB, Nik-Zainal S, Wedge DC, et al; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain. Signatures of mutational processes in human cancer. *Nature*. 2013;500(7463):415-421. doi:10.1038/nature12477

53. Helgason H, Rafnar T, Olafsdottir HS, et al. Loss-of-function variants in ATM confer risk of gastric cancer. *Nat Genet*. 2015;47(8):906-910. doi:10.1038/ng.3342

54. Hsu FC, Roberts NJ, Childs E, et al. Risk of pancreatic cancer among individuals with pathogenic variants in the ATM gene. *JAMA Oncol*. 2021;7(11):1664-1668. doi:10.1001/jamaoncol.2021.3701

55. Carlo MI, Ravichandran V, Srinavasan P, et al. Cancer susceptibility mutations in patients with urothelial malignancies. *J Clin Oncol*. 2020;38(5):406-414. doi:10.1200/JCO.19.01395

56. Bazinet A, Heath J, Chong AS, et al. Common clonal origin of chronic myelomonocytic leukemia and B-cell acute lymphoblastic leukemia in a patient with a germline *CHEK2* variant. *Cold Spring Harb Mol Case Stud*. 2021;7(3):a006090. doi:10.1101/mcs.a006090

57. Rudd MF, Sellick GS, Webb EL, Catovsky D, Houlston RS. Variants in the *ATM-BRCA2-CHEK2* axis predispose to chronic lymphocytic leukemia. *Blood*. 2006;108(2):638-644. doi:10.1182/blood-2005-12-5022

58. Moore NS, Aldubayan SH, Taylor-Weiner A, et al. Inherited DNA repair and cell cycle gene defects in chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(15)(suppl):1508. doi:10.1200/JCO.2019.37.15_suppl.1508

59. Bick AG, Weinstock JS, Nandakumar SK, et al; NHLBI Trans-Omics for Precision Medicine Consortium. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020;586(7831):763-768. doi:10.1038/s41586-020-2819-2

60. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498. doi:10.1056/NEJMoa1408617

61. Kwan TT, Oza AM, Tinker AV, et al. Preexisting *TP53*-variant clonal hematopoiesis and risk of secondary myeloid neoplasms in patients with high-grade ovarian cancer treated with rucaparib. *JAMA Oncol*. 2021;7(12):1772-1781. doi:10.1001/jamaoncol.2021.4664

62. Mann CJ. Observational research methods: research design II: cohort, cross sectional, and case-control studies. *Emerg Med J*. 2003;20(1):54-60. doi:10.1136/emj.20.1.54

63. Wasylishen AR, Sun C, Chau GP, et al. Men1 maintains exocrine pancreas homeostasis in response to inflammation and oncogenic stress. *Proc Natl Acad Sci U S A*. 2020;117(12):6622-6629. doi:10.1073/pnas.1920017117

64. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol*. 2015;12(10):584-596. doi:10.1038/nrclinonc.2015.105

65. Casorelli I, Pannellini T, De Luca G, et al. The Mutyh base excision repair gene influences the inflammatory response in a mouse model of ulcerative colitis. *PLoS One*. 2010;5(8):e12070. doi:10.1371/journal.pone.0012070

66. González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids*. 2012;77(4):300-305. doi:10.1016/j.steroids.2011.12.003

67. Bastarache L, Hughey JJ, Goldstein JA, et al. Improving the phenotype risk score as a scalable approach to identifying patients with mendelian disease. *J Am Med Inform Assoc*. 2019;26(12):1437-1447. doi:10.1093/jamia/ocz179

68. Bastarache L, Hughey JJ, Hebbring S, et al. Phenotype risk scores identify patients with unrecognized Mendelian disease patterns. *Science*. 2018;359(6381):1233-1239. doi:10.1126/science.aal4043

69. Roy R, Chun J, Powell SN. *BRCA1* and *BRCA2*: different roles in a common pathway of genome protection. *Nat Rev Cancer*. 2011;12(1):68-78. doi:10.1038/nrc3181

70. Denny JC, Rutter JL, Goldstein DB, et al; All of Us Research Program Investigators. The "All of Us" research program. *N Engl J Med*. 2019;381(7):668-676. doi:10.1056/NEJMsr1809937