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ARTICLE

Pathogenic variants in arteriopathy genes detected in a targeted sequencing study: Penetrance and 1-year outcomes after return of results

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ABSTRACT

Purpose: We estimated the penetrance of pathogenic/likely pathogenic (P/LP) variants in arteriopathy-related genes and assessed near-term outcomes following return of results.
Methods: Participants ($N = 24,520$) in phase III of the Electronic Medical Records and Genomics network underwent targeted sequencing of 68 actionable genes, including 9 genes associated with arterial aneurysmal diseases. Penetrance was estimated on the basis of the presence of relevant clinical traits. Outcomes occurring within 1 year of return of results included new diagnoses, referral to a specialist, new tests ordered, surveillance initiated, and new medications started.
Results: P/LP variants were present in 34 participants. The average penetrance across genes was 59%, ranging from 86% for *FBN1* variants to 25% for *SMAD3*. Of 16 participants in whom results were returned, 1-year outcomes occurred in 63%. A new diagnosis was made in 44% of the participants, 56% were referred to a specialist, a new test was ordered in 44%, surveillance was initiated in 31%, and a new medication was started in 31%.
Conclusion: Penetrance of P/LP variants in arteriopathy-related genes, identified in a large, targeted sequencing study, was variable and overall lower than that reported in clinical cohorts. Meaningful outcomes within the first year were noted in 63% of participants who received results.

Introduction

A consequence of population-scale genome sequencing initiatives is the detection of pathogenic/likely pathogenic (P/LP) variants in actionable genes.[1] At the time this study was initiated, the American College of Medical Genetics and Genomics (ACMG) had listed 59 actionable genes for which medical management guidelines were available for

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individuals with P/LP variants.[2] The list has since been expanded to 73 genes,[3] and the ACMG recommends that laboratories report P/LP variants in these genes when detected as part of clinical testing. However, guidelines for returning these variants as part of research studies are not established.

Among actionable genes on the ACMG list are those associated with arterial aneurysmal disease, including *FBN1, SMAD3, TGFBR1, TGFBR2*, *COL3A1, ACTA2, SMAD4,* and *MYH11*.[4] Hereditary arteriopathies can present as arterial rupture or dissection[5] and can be syndromic (associated with extracardiac manifestations) or nonsyndromic.[6] Marfan syndrome, Loeys-Dietz syndrome (LDS), and vascular Ehlers-Danlos syndrome (vEDS) (type IV) constitute the main syndromic aortopathies, whereas hereditary thoracic aortic aneurysmal disease (HTAAD) and thoracic aortic aneurysm associated with bicuspid aortic valve are examples of nonsyndromic disorders.

Detection of a P/LP variant associated with aneurysmal disease may trigger the initiation of surveillance programs, which include serial imaging, and medical management, including prescription of beta-blockers or angiotensin receptor blockers (ARBs) to lower blood pressure and reduce aneurysm growth rate.[7] However, the penetrance of P/LP variants in arterial aneurysm-related genes in the genotype-first setting is unknown, as are outcomes consequent to the return of such findings.[8] As a result, the management of arteriopathy-related P/LP variants detected in individuals undergoing genome sequencing as part of large-scale projects is unclear.

We attempted to address these knowledge gaps using data from phase III of the Electronic Medical Records and Genomics (eMERGE) network, a consortium that links genomic and phenotypic data for genomic discovery and implementation.[9,10] Our objectives were to estimate the penetrance of P/LP variants in arteriopathy genes and ascertain the 1-year outcomes after return of results (RoR) to study participants. Such data are needed to inform the management of participants in large-scale sequencing projects in whom such variants are detected, given the potential for fatal/morbid complications, such as aneurysm rupture or dissection.

Materials and Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.[11]

Study design

The eMERGE network consists of 10 academic institutions across the United States funded by the National Human Genome Research Institute, with the purpose of combining genomic data with electronic health record (EHR)-derived phenotypic data for genomic discovery and genomic medicine implementation.[9,10] The design of the eMERGESeq genomic medicine implementation study, which recruited individuals for targeted genomic sequencing, has been previously described.[12,13]

Data from the following 9 eMERGE network sites were included in our study: Mayo Clinic, Geisinger, Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Vanderbilt University Medical Center, Harvard University, Northwestern University, Columbia University, and University of Washington.

Setting

Participants were recruited from biobanks established at eMERGE sites.[13] The Institutional Review Boards at each site approved the study before data collection. Two sites (Cincinnati Children`s Hospital Medical Center and Children`s Hospital of Philadelphia) enrolled both children and adult participants. Other sites only enrolled adult individuals. Three sites (Harvard University, Vanderbilt University Medical Center, and Cincinnati Children's Hospital Medical Center) enrolled unselected participants. At other sites, cohorts were enriched for cancer, hyperlipidemia, or neurologic conditions or included referrals from specific clinics (Supplemental Table 1).[13] At 1 site (Geisinger), the cohort was enriched for patients with actionable findings (genotypes) detected in a previous study. We excluded this site when estimating prevalence. None of the sites recruited individuals on the basis of the presence of arterial aneurysmal disease.

Participants

Participants ($N = 24{,}520$) were ascertained on the basis of each site's specific strategy and demographics to undergo targeted sequencing of 68 actionable genes,[14,15] 59 genes on the ACMG list at that time[16] and 9 additional genes nominated by eMERGE investigators.[12,13] Targeted sequencing was performed by Baylor College of Medicine Human Genome Sequencing Center and the Broad Institute and Partners Laboratory for Molecular Medicine, both Central Laboratory Improvement Amendment–certified facilities.[15] Detailed descriptions of sequencing methods and variant annotation have been previously published.[1,12,17] After identification of actionable variants, the Baylor College of Medicine Human Genome Sequencing Center and the Partners Laboratory for Molecular Medicine laboratories confirmed these variants by Sanger sequencing and issued clinical reports. Only P/LP variants and not variants of uncertain significance were returned. Therefore, for variants of uncertain significance, phenotyping data were not ascertained. The reports were reviewed by site investigators before return to participants by a genetic counselor (most sites), letter, or other participant choice methods.[15]

Sequence data

Participants from 9 clinical sites included in this study underwent targeted sequencing of actionable genes using the eMERGEseq panel, which included 9 genes associated with inherited arterial aneurysmal diseases: *FBN1* (Marfan syndrome); *SMAD3, TGFBR1,* and *TGFBR2* (LDS); *ACTA2, SMAD4, MYH11,* and *MYLK* (HTAAD); and *COL3A1* (vEDS).

The ClinGen framework was used for variant annotation by the two Central Laboratory Improvement Amendment–certified genomic laboratories, along with previous case studies and literature review.[13] Variant pathogenicity was assigned on the basis of the ACMG/Association for Molecular Pathology variant classification guidelines.[1]

RoR

A total of 68 genes were deemed actionable by eMERGE investigators, and participants with P/LP variants in these genes were contacted and informed that a medically actionable result had been detected and were invited to discuss the result during a genetic counseling. P/LP variants were returned to adult participants with contact information. Participants who declined or were unable to see the genetic counselor or follow up with a clinician as well as individuals aged <18 years were excluded from analysis of outcomes, but their data were used for estimating penetrance.

Data sources

There were 34 participants with P/LP variants in arteriopathy-associated genes who were included in this report (Figure 1). At each participating eMERGE site, data including demographics or previous diagnoses were abstracted from the EHR at the time of RoR.[18]

Penetrance

Phenotype data were reviewed manually at each site and entered into a REDCap survey developed by Mayo investigators to assess the penetrance of arteriopathy genes. A list of traits relevant to arterial aneurysmal disease was compiled (Supplemental Table 2). In addition, we assessed whether the International Classification of Diseases (ICD)-9 and 10 billing codes for relevant traits had been recorded before RoR. We thus combined manual EHR review with automated ascertainment of ICD-9 and 10 codes. Aortic and other arterial aneurysm/dissection were ascertained on the basis of available echocardiography, computed tomography scan, or magnetic resonance imaging (MRI) findings at any time in the EHR.

A *z*-score for ascending aortic dimension was calculated using nomograms from Devereux et al[19] that take into account aortic root diameter and the predicted measure on the basis of age, sex, and body surface area. A *z*-score ≥ 2 was considered an aortic aneurysm.

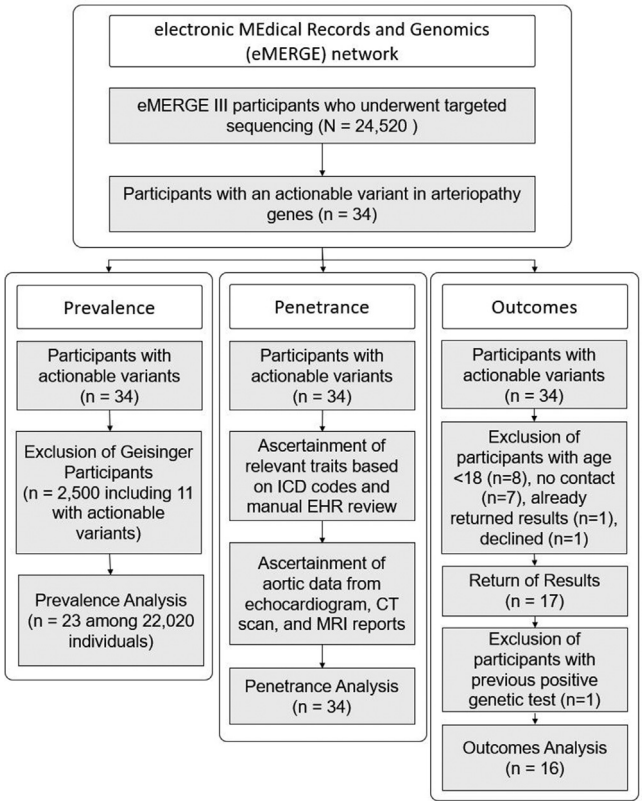

Figure 1 Overview of participants included in penetrance and outcome analyses. In phase III of eMERGE, 24,520 participants underwent targeted sequencing of 68 actionable genes, including 9 arteriopathy-associated genes (*FBN1, SMAD3, TGFBR1, TGFBR2*, *ACTA2, SMAD4, MYH11, MYLK*, and *COL3A1*). Electronic health records were reviewed for participants with a pathogenic/likely pathogenic variant to assess the presence of relevant clinical traits and penetrance estimation. Outcome analysis was performed for participants with returned results if they were aged >18 years and had no previous genetic testing before this study. *Geisinger participants were excluded from estimation of prevalence but were included in penetrance and outcomes analyses. eMERGE, Electronic Medical Records and Genomics.

A P/LP variant was considered penetrant if the relevant diagnosis or clinical trait was noted in the EHR. Penetrance in those who did not receive their results was determined on the basis of the presence of relevant ICD codes in the period before RoR.

Analysis of outcomes

A REDCap survey developed by the Mayo investigators was used to capture outcomes by study personnel at each site. At each site, EHRs were reviewed to complete this survey and capture outcomes during the year after RoR. Outcomes included referral to a specialist, new tests ordered, new diagnosis recorded, new medication started, and surveillance initiated. Outcomes were classified as process, intermediate, and clinical outcomes[8] on the basis of a framework suggested by Williams et al[20] and Peterson

et al.[21] Referral to a specialist, ordering new tests, or initiation of surveillance were considered process outcomes. Intermediate outcomes included making new diagnoses or having positive findings on tests. Clinical outcomes included modification of drug therapy or performing a risk-reducing surgery or procedure. Only outcomes with clear attribution to RoR were included. One participant with a known phenotype and a previous genetic test was excluded from outcomes analysis. Other participants with a previously known phenotype before RoR and no previous genetic tests ($n = 3$) were reviewed for outcomes.

Bias

Most (87%) of the participants were of European ancestry. Because participants were enrolled from eMERGE site biobanks, volunteer and healthy participant bias is possible. Some participants were ascertained through specialty clinics, and this could also be a source of bias.

Study size

This study included 24,520 individuals enrolled at different eMERGE sites. Of these, 5,976 participants were aged <18 years at the time of enrollment/RoR.[13]

Statistical methods

Data for penetrance estimation and outcome analyses are reported as means and frequencies. The 95% CI for a proportion was calculated. Comparison of proportions was done using χ^2 and Fisher's exact tests. All tests were 2 sided. $P < .05$ was considered statistically significant.

Results

Across the eMERGE network, P/LP variants in arteriopathy-related genes were present in 34 of 24,520 individuals. In all, 28 different arteriopathy-related P/LP variants were identified. After exclusion of Geisinger participants (this site recruited participants on the basis of the presence of actionable variants), 23 of 22,020 participants had P/LP arteriopathy variants, giving a prevalence of 1:957. The 34 individuals with arteriopathy-related P/LP variants included 14 individuals with variants related to Marfan syndrome, 6 individuals with variants related to LDS, 9 individuals with variants related to HTAAD, and 5 individuals with variants related to vEDS. The median age at the time of RoR was 45.9 years, ranging from 11 to 69 years; 56% were females, and 87% were of European ancestry. Results could not be returned to 17 participants. Of 17 patients with returned results, family history of aneurysmal disease/dissection was present in 8 (47%); 4 participants had a previous clinical diagnosis of Marfan syndrome, but only 1 of these 4 had previous genetic testing.

Prevalence of relevant clinical traits

Of 34 participants with P/LP variant in an arteriopathy gene, a relevant clinical trait was present in 20 (59%, CI = 41-75%) (Table 1, Supplemental Table 3). A total of 14 (41%, CI = 25-59%) participants had aortic dilation/

Table 1 Penetrance of pathogenic/likely pathogenic variants in arteriopathy genes

	Returned					Total				
Gene	*N*	Age[a]	Sex	Clinical Trait Present	Penetrance	*n*	Age[a]	Sex	Clinical Trait Present	Penetrance
ACTA2	7	47	0 M 7 F	4	0.57	7	47	0 M 7 F	4	0.57
COL3A1	2	68	1 M 1 F	1	0.5	5	39	2 M 3 F	2	0.4
FBN1	5	47	3 M 2 F	5	1.0	14	42	6 M 8 F	12	0.86
SMAD3	2	37	2 M 0 F	1	0.5	4	31	4 M 0 F	1	0.25
SMAD4	1	28	0 M 1 F	1	1.0	2	24	1 M 1 F	1	0
TGFBR1	0	—	—	—	—	1	15	0 M 1 F	0	0
TGFBR2	0	—	—	—	—	1	44	0 M 1 F	0	0
	17	47	6 M 11 F	12	0.71	34	40	13 M 21 F	20	0.59

A total of 9 arteriopathy-associated genes were sequenced in eMERGE phase III participants ($N = 24,520$). Pathogenic/likely pathogenic variants were found in 7 genes and in 34 participants. Of these participants, a relevant clinical trait was present in 20 (59%). Results were returned in 17 participants, but electronic health records were reviewed for all the 34 participants to estimate penetrance.

eMERGE, Electronic Medical Records and Genomics; *F*, female; *M*, male.

[a]Average age.

aneurysm/dissection, including 9 participants with *FBN1* variants, 3 with *ACTA2* variants, 1 with a *COL3A1* variant, and 1 with a *SMAD3* variant. Among 14 participants without a related clinical trait noted in the EHR, aortic imaging data were not available for 8 individuals. We considered the variants in these individuals as nonpenetrant on the basis of the absence of associated ICD codes. There was no statistically significant difference in the presence of clinical traits between participants with missense and nonmissense variants (53% vs 65%, $P = .73$). The proportion of participants with a relevant clinical trait was significantly higher in *FBN1* P/LP variants than for other variants (86% vs 40%, $P = .013$).

A relevant clinical trait was observed in 12 of 14 participants (86%, CI = 57-98) with *FBN1* P/LP variants associated with Marfan syndrome (mean age of 42 years at the time of RoR) (Table 2). In total, 7 participants had a clinical diagnosis of aortic aneurysm on the basis of the pre-RoR ICD codes. Of the *FBN1* variants, 7 were truncating (4 nonsense and 3 frameshift variants), 6 were missense, and 1 was a splice donor variant. All participants with truncating variants had features of Marfan syndrome, and 5 had aortic involvement; 4 of 6 of missense variants had clinical features of Marfan syndrome, and 3 of 6 had aortic involvement (Table 2).

Of the 6 participants with P/LP variants associated with LDS (mean age of 30 years), only 1 was considered penetrant; a male in his 30s with a pathogenic variant in *SMAD3* had aortic ectasia (aortic root of 3.8 cm, z-score = 1 .73) and mitral valve prolapse and received a clinical diagnosis of LDS after RoR. Three participants with variants in *SMAD3*, 1 participant with variants in *TGFBR1*, and 1 participant with variants in *TGFBR2* did not have any relevant clinical feature in the EHR.

Of the 9 participants with P/LP variants associated with HTAAD (mean age of 42 years), 4 of 7 *ACTA2* P/LP variants were considered penetrant (57%, CI = 18%-90%); in 2 patients, mild aortic ectasia was identified on MRI; 1 had a dilated aortic root of 3.8 cm (z-score = 2.83) on echocardiogram; and 1 had a personal history of myocardial infarction, coronary artery stent placement, and a family history of aortic aneurysm. All participants with *ACTA2* P/LP variants were from 1 center but were unrelated. The 2 patients with *SMAD4* P/LP variants did not manifest aortic aneurysm/dissection. However, a clinical diagnosis of hereditary hemorrhagic telangiectasia was made in 1 participant with a P/LP *SMAD4* variant, who had pulmonary arteriovenous malformations and an inflammatory colon polyp but no aortic dilation. We considered this variant as penetrant. No P/LP variants in *MYH11* and *MYLK* were identified.

Of the 5 participants with variants related to vEDS (*COL3A1*) (mean age of 38.6 years), 1 had thoracic aortic ectasia, aortic valve dysfunction, intestinal torsion, and easy bruising. Scoliosis and a vEDS ICD code were identified in another participant with *COL3A1* who did not receive the result (penetrance of *COL3A1* variants for vEDS was 40%).

Outcomes

Of 34 participants with a P/LP variant in an arteriopathy gene, results could not be returned to 17 participants; the study team could not contact 7 participants, and 1 participant declined to attend the RoR session; 8 other participants were children and were excluded because of the study design (outcomes were assessed only in adult participants). However, results were placed in EHR for all of these participants, per study protocol. One participant knew the results beforehand and chose not to attend the RoR session. For 1 participant, results were returned, but he had a known phenotype and a previous genetic test and was therefore excluded from the outcomes analysis.

Of 16 participants who received results and were included in outcomes analysis, 9 (56%, CI = 30%-80%) had process outcomes; all the 9 were referred to a specialist, 7 (44%, CI = 20%-70%) had new tests ordered, and 5 (31%, CI = 11%-59%) were enrolled in periodic surveillance. Seven participants (44%, CI = 20%-70%) had an intermediate outcome, ie, receiving a new clinical diagnosis after RoR, and 5 (31%, CI = 11%-59%) had a clinical outcome (change in medical treatment) (Table 3, Supplemental Table 4). Of 6 participants with no outcomes observed, 4 appeared to have taken no action after RoR despite receiving recommendations from their providers. Five participants were interested in cascade testing of their family members, and invitations for screening were sent to their family members. Below, we provide additional details by type of arteriopathy.

Marfan syndrome

Of 14 participants with P/LP variants in *FBN1*, results were returned in 5 individuals, 4 of whom had been previously diagnosed with Marfan syndrome. Only 1 of these participants (aged 45 years) had previously completed genetic testing. This participant was excluded from the outcomes analysis. The 1-year outcomes in the 4 remaining participants were as follows: a new clinical diagnosis was made in 1; 1 was referred for genetic and cardiology consultations; and 1 underwent new tests on the basis of RoR, including a transthoracic echocardiogram; 2 participants who had been receiving angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers before RoR continued these without change.

LDS

Of 6 participants with P/LP variants in genes associated with the LDS (*SMAD3*, *TGFBR1*, and *TGFBR2*), results were returned in 2. None had been diagnosed or had previous genetic testing. These two participants were referred for genetic counseling. A family history of aneurysms was present in the first participant referred to a medical geneticist; echocardiography was performed after RoR, which showed an aortic diameter of 3.6 cm. Clinical diagnosis was

Table 2 Pathogenic/likely pathogenic variants in arteriopathy genes and associated clinical traits

Gene	Variant	Molecular Consequence	Amino Acid Change	Interpretation	RoR	Penetrant	Age	Aortic Involvement	Extraaortic Manifestations	Clinical Syndrome
FBN1	NM_000138.5:c.7C>T	Nonsense	p.Arg3Ter	Pathogenic	Yes	Yes	58	Ectasia	Yes	Marfan Syndrome
	NM_000138.5:c.4615C>T	Nonsense	p.Arg1539Ter	Pathogenic	Yes	Yes	45	Aneurysm	No	Marfan syndrome
	NM_000138.5:c.4567C>T	Nonsense	p.Arg1523Ter	Pathogenic/Likely pathogenic	No	Yes	46	Aneurysm	No	Marfan syndrome
	NM_000138.5:c.7656C>A	Nonsense	p.Cys2552Ter	Pathogenic	No	Yes	67	None	Yes	Marfan syndrome
	NM_000138.5:c.4168_4171del	Frameshift	p.Leu1390fs	Pathogenic	Yes	Yes	45	Aneurysm Dissection	Yes	Marfan syndrome
	NM_000138.5:c.1948dup	Frameshift	p.Arg650fs	Likely pathogenic	No	Yes	61	Aneurysm	No	Marfan syndrome
	NM_000138.5:c.7217_7226delinsTACAGA	Frameshift	p.Cys2406fs	Likely pathogenic	No	Yes	18	None	Yes	Marfan syndrome
	NM_000138.5:c.3656A>G	Missense	p.Tyr1219Cys	Pathogenic/Likely pathogenic	Yes	Yes	42	Aneurysm	Yes	Marfan syndrome
	NM_000138.5:c.2495G>A	Missense	p.Cys832Tyr	Pathogenic/Likely pathogenic	No	Yes	56	Aneurysm Dissection	Yes	Marfan syndrome
	NM_000138.5:c.1633C>T	Missense	p.Arg545Cys	Pathogenic	No	Yes	42	None	Yes	Marfan syndrome
	NM_000138.5:c.3413G>A	Missense	p.Cys1138Tyr	Likely pathogenic	No	Yes	16	Aneurysm	Yes	Marfan syndrome
	NM_000138.5:c.7754T>C	Missense	p.Ile2585Thr	Pathogenic/Likely pathogenic	No	No	24	None	No	—
	NM_000138.5:c.7016G>A	Missense	p.Cys2339Tyr	Likely pathogenic	No	No	23	None	No	—
	NM_000138.5:c.4816+2T>C	Splice donor		Pathogenic	Yes	Yes	47	Dissection	Yes	Marfan syndrome
ACTA2	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	Yes	54	Ectasia	No	HTAAD
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	Yes	46	Ectasia	No	HTAAD
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	Yes	33	Aneurysm	No	HTAAD
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	Yes	46	None	Yes	HTAAD
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	No	61	None	No	—
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	No	58	None	No	—
	NM_001613.4:c.353G>A	Missense	p.Arg118Gln	Pathogenic/Likely pathogenic	Yes	No	33	None	No	—
COL3A1	NM_000090.4:c.2267G>A	Missense	p.Gly756Glu	Pathogenic/Likely pathogenic	No	Yes	16	None	Yes	vEDS
	NM_000090.4:c.1509+2T>C	Splice donor		Likely pathogenic	Yes	Yes	69	Ectasia	Yes	vEDS
	NM_000090.4:c.1258G>A	Missense	p.Gly420Ser	Pathogenic/Likely pathogenic	No	No	17	None	No	—
	NM_000090.4:c.4087C>T	Nonsense	p.Arg1363Ter	Pathogenic/Likely pathogenic	Yes	No	67	None	No	—
	NM_000090.4:c.1173del	Frameshift	p.Pro392fs	Likely pathogenic	No	No	24	None	No	—
SMAD3	Deletion of exons 7-9			Pathogenic	Yes	Yes	37	Ectasia	Yes	LDS
	NM_005902.4:c.206+1G>C	Splice donor		Likely pathogenic	Yes	No	50	None	No	—
	NM_005902.4:c.715G>A	Missense	p.Glu239Lys	Likely pathogenic	No	No	11	None	No	—
	NM_005902.4:c.1102C>T	Nonsense	p.Arg368Ter	Pathogenic	No	No	24	None	No	—
SMAD4	NM_005359.6:c.1498A>G	Missense	p.Ile500Val	Pathogenic	No	No	20	None	No	—
	NM_005359.6:c.1245_1248del	Frameshift	p.Asp415fs	Pathogenic	Yes	Yes	28	None	Yes	Hereditary hemorrhagic telangiectasia
TGFBR1	NM_004612.4:c.683_685del	Microsatellite	p.Glu228del	Pathogenic	No	No	15	None	No	—
TGFBR2	NM_003242.6:c.170-2A>G	Splice donor		Likely pathogenic	No	No	44	None	No	—

A total of 34 participants had a pathogenic/likely pathogenic variant in arteriopathy-associated genes. ICD codes related to arterial aneurysm/dissection were checked for all variants. ICD codes related to clinical traits of syndromes related to each gene were also checked.

HTAAD, familial thoracic aortic aneurysm disease; *ICD*, International Classification of Diseases; *LDS*, Loeys-Dietz syndrome; *RoR*, return of results; *vEDS*, vascular Ehlers-Danlos syndrome.

not made in this participant, but periodic surveillance was initiated. The second participant with known mitral valve abnormalities and paroxysmal atrial fibrillation was referred to a cardiologist and a vascular surgeon after medical genetics consultation; a cardiac MRI ordered after RoR showed aortic ectasia with a diameter of 3.8 cm (z-score = 1.73). This participant received a clinical diagnosis of LDS and was started on a beta-blocker and an ARB.

Hereditary thoracic aortic aneurysm disease

Seven participants had a P/LP variant in *ACTA2* (NM_001613.4:c.353G>A). These participants were not related at the level of third-degree familial relationships. None had a previous clinical diagnosis or genetic testing for HTAAD. Four participants had a family history of aneurysms, including aortic dissection or aneurysm, intracranial aneurysm, and abdominal aortic aneurysm. Results were returned to all the 7 participants. Four were referred for genetic consultation, 3 of whom were also referred for cardiology consultation at the same time. The fourth patient was referred for cardiology consultation a few months later; 4 had new tests ordered on the basis of RoR, including 2 transthoracic echocardiograms, 2 magnetic resonance angiograms, and 1 computed tomography angiogram (1 participant had both echocardiogram and magnetic resonance angiograms); and 3 had a change in their medical treatment (beta-blocker initiated in 1 and ACEI initiated in 3). One participant was on a beta-blocker and ACEI therapy before RoR, and the treatment was continued. Periodic surveillance was initiated in 4 participants.

The participant with a P/LP *SMAD4* variant and known hereditary hemorrhagic telangiectasia received results, but no outcomes were observed during the 1-year follow-up.

vEDS (type IV)

Results were returned in 2 participants with P/LP variants in *COL3A1,* associated with vEDS (type IV). Neither carried a diagnosis of the condition. Both individuals completed genetic counseling. The first had no clinical features of vEDS but had a family history of spontaneous coronary artery dissection in an offspring in their 30s, and the other had aortic ectasia, a history of intestinal torsion requiring surgery, and aortic valve regurgitation. A new diagnosis of vEDS was made in the latter participant, and an ARB was started.

Discussion

In a targeted sequencing study of 24,520 participants, conducted as part of eMERGE phase III, arteriopathy-related P/LP variants were detected in 34 participants (prevalence of 1:957 after correction for ascertainment bias at 1 site).

Table 3 One-year outcomes after RoR (n = 16)

Outcome	Type	Number
Process	Referral to a specialist	9
	New tests based on RoR	7
	Surveillance initiated	5
Intermediate	New diagnosis	7
	Marfan syndrome	1
	LDS	1
	vEDS	1
	HTAAD	4
Clinical	Medication started/altered	5
	BB	2
	ACEI/ARB	5
	Participants with at least one outcome	10

Results were returned to 17 participants. One participant with previous genetic testing and clinical diagnosis was excluded from outcome analysis. Near-term outcomes were divided into process (referral to a specialist, ordering new tests, initiation of surveillance), intermediate (new diagnosis), and clinical (initiation of new treatment) outcomes.

ACEI, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BB*, beta-blocker; *HTAAD*, familial thoracic aortic aneurysm disease; *LDS*, Loeys-Dietz syndrome; *vEDS*, vascular Ehlers-Danlos syndrome.

Penetrance of the arteriopathy-related variants was 59% overall, ranging from 86% in Marfan syndrome variants to 25% in *SMAD3*-related LDS variants. Meaningful short-term outcomes occurred in 63% of the 16 participants who received results, including referral to a specialist, receipt of a new clinical diagnosis, initiation of a surveillance program, or change in medical treatment.

A consequence of large-scale genomic sequencing programs is the discovery of P/LP variants in actionable genes. The clinical implications of such findings remain unclear.[22] Routine genetic screening for diseases, ie, the genome first approach, can detect P/LP variants that may have lower penetrance[23] than often reported in the clinical setting. Generally, it is believed that estimates of penetrance from a population-sequencing study represent the floor and that those in the clinical setting represent the ceiling of penetrance estimates. However, robust estimates of the penetrance of P/LP variants detected in large-scale genomic sequencing studies are not available.[24,25] These estimates can help patients, family members, and clinicians to better understand the implications of the results and guide them in the process of health-related decision making, including family planning.

Linkage of genomic data to the EHR enabled us to ascertain the relevant clinical traits that we used as a surrogate for penetrance. High penetrance of *FBN1* P/LP variants (~86%) has been previously reported.[26] Most of these participants received the diagnosis of Marfan syndrome in the years before the eMERGE study. The diagnosis of aortic aneurysm in these participants was based on ICD codes in the EHR. The 2 patients with P/LP variants in *FBN1* and no recorded clinical features were young adults (aged <25 years) who were not available to receive results and therefore did not undergo aortic imaging. We found lower than

expected penetrance estimates for P/LP variants in LDS genes;[27] of the 3 participants with no clinical phenotype, 1 was aged 50 years, which makes the future diagnosis of LDS unlikely.[28] The other 2 participants were aged 11 and 28 years and could yet manifest the phenotype. Of the 7 participants with a P/LP variant in *ACTA2*, the most common gene associated with HTAAD,[29,30] aortic root dilation was observed in 3 (Z-score was 2.8 in 1 and not available in other 2). Penetrance of vEDS variants was also lower than previously reported,[31] with only 2 of 5 participants with a P/LP variant manifesting the classical features or having a relevant ICD code.

Our estimates of penetrance should be considered preliminary, and additional studies are needed. Absence of relevant traits associated with a P/LP variant may be due to several reasons, including truly reduced penetrance, absence of phenotyping information, such as imaging data, an insufficient short-term follow-up period, variant misclassification, or survival bias. We did not have sufficient numbers to assess whether the type of a P/LP variant was associated with penetrance, as others have reported.[29,32] However, for *FBN1*, our results did suggest that the type of P/LP variant might influence phenotype. *FBN1*-truncating P/LP variants were all penetrant, and most had aortic aneurysm or dissection, whereas half of the participants with missense P/LP *FBN1* variant did not have aortic involvement.

Both genes and variants can be reclassified as new knowledge emerges.[1] At the time of writing, none of the P/LP arteriopathy variants identified in this study have been reclassified by the 2 sequencing laboratories. However, the list of the actionable genes has been expanded by the ACMG to now include 73 genes.[4] Notably, *MYLK* has been removed from the actionable list, and 14 new genes have been added, none of which are associated with arteriopathy.[4] The decision regarding omitting *MYLK* was based on the rarity of P/LP variants in this gene and on the fact that these are associated with spontaneous arterial dissection in the absence of aneurysmal disease so that early detection is not feasible.[3]

Measuring outcomes after return of genomic results is important for informed adoption of genomic medicine.[21] Outcomes after return of P/LP penetrant variants in arteriopathy genes have not been previously assessed.[33] Meaningful short-term outcomes occurred in 63% of the 16 participants who received results, including referral to a specialist, receipt of a new clinical diagnosis, initiation of a surveillance program, or change in medical treatment. The most common clinical outcome was starting a new blood pressure medication such as an ARB or beta-blocker in 5 participants (29%) to decrease the risk of aneurysm formation/expansion. HTAAD was the most common new diagnosis, and ACEI/ARB blocker was the most common newly prescribed drug class. To generate an evidence-based framework for implementation of genomic sequencing data in clinical practice, a meta-analysis of results from multiple ongoing genomic sequencing studies will be necessary.[34,35]

Data for penetrance as well as outcomes after RoR are needed to guide patient and provider decisions. Hereditary arteriopathies can present with morbid/fatal complications, and therefore detection of P/LP variants in arteriopathy genes necessitates genetic counseling of patient and family members and consideration of further diagnostic workup and initiation of surveillance.

With ready availability and decreasing costs, genome sequencing is used increasingly for research and clinical purposes, and several large biobanks have linked exome/whole-genome sequencing data to EHR phenotypic data. Although identification of variant pathogenicity has been a focus of analyzing the biobank data, this study also assessed the effect of RoR on patient outcomes. Our results can help inform the return of actionable results in biobank studies. Establishing the clinical utility of such an approach will require additional studies.

Study limitations

Several limitations of our study should be mentioned. The data we used are observational, the number of participants with arteriopathy-associated P/LP variants (34 of 24,520 individuals) was small, and ethnic diversity was limited. However, reporting such results is important to build the evidence base for penetrance estimates and outcomes in large-scale sequencing projects. We estimated penetrance primarily on the basis of manual EHR review. Most eMERGE sites are tertiary care centers and may not be representative of other healthcare settings.[36] Some of the site cohorts were enriched for specific phenotypes such as colorectal polyps or neurologic conditions and thus may not be representative of the general population. We assessed short-term outcomes, and further studies to assess long-term outcomes and changes in health status are still needed. Costs and health care utilization, psychosocial impacts, and sharing of genomic results with family members were not evaluated.

Conclusion

In a cohort of 24,520 individuals who underwent targeted sequencing of medically actionable genes, the prevalence of arteriopathy-related P/LP variants was 1 in 957 after correcting for ascertainment bias. On average, the penetrance of these variants was 59%, ranging from 86% in *FBN1* to 25% in *SMAD3*. Our findings are consistent with the lower penetrance of P/LP variants identified as part of a genotype first approach than of P/LP variants identified in the clinical setting. Within a Bayesian framework, the posterior probability of a variant being penetrant is low because arteriopathies are uncommon in the general population. However, given the serious complications of arteriopathy, the presence of P/LP variants in arteriopathy genes requires genetic counseling and potential additional measures. In this study, detection of P/LP variants in arteriopathy genes led to outcomes such as early detection of a disease trait, risk-reducing medical treatment, or initiation of surveillance in 63% of participants who received results. Additional data

from ongoing large-scale sequencing initiatives are needed to build on the findings reported in this paper.

Data Availability

Data is deposited in dbGaP (accession code phs001616.v2.p2) at website https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001616.v2.p2

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Ethics Declaration

Participants were asked to complete a study consent form and health questionnaires and provide a blood sample (if an existing sample was not available) to participate in this study. This study and the informed consent process were approved by the Mayo Institutional Review Board (as the main Institutional Review Board of the first and corresponding authors' institutions) as well as other Institutional Review Boards at the Electronic Medical Records and Genomics sites. More information about the ethical considerations in Electronic Medical Records and Genomics phase III study, including the Mayo Clinic Biobank, are provided at https://pubmed.ncbi.nlm.nih.gov/29301385/. Information about the Mayo Clinic Biobank's collection and enrollment methods are provided at https://pubmed.ncbi.nlm.nih.gov/24001487/. The link to the Mayo Clinic Biobank website is as follows: https://www.mayo.edu/research/centers-programs/mayo-clinic-biobank/overview.

Conflict of Interest

The authors declare no conflict of interest.

Additional Information

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