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ORIGINAL ARTICLE

A study of elective genome sequencing and pharmacogenetic testing in an unselected population

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Abstract

Background: Genome sequencing (GS) of individuals without a medical indication, known as elective GS, is now available at a number of centers around the United States. Here we report the results of elective GS and pharmacogenetic panel testing in 52 individuals at a private genomics clinic in Alabama.

Methods: Individuals seeking elective genomic testing and pharmacogenetic testing were recruited through a private genomics clinic in Huntsville, AL. Individuals underwent clinical genome sequencing with a separate pharmacogenetic testing panel.

Results: Six participants (11.5%) had pathogenic or likely pathogenic variants that may explain one or more aspects of their medical history. Ten participants (19%) had variants that altered the risk of disease in the future, including two individuals with clonal hematopoiesis of indeterminate potential. Forty-four participants (85%) were carriers of a recessive or X-linked disorder. All individuals with pharmacogenetic testing had variants that affected current and/or future medications.

Conclusion: Our study highlights the importance of collecting detailed phenotype information to interpret results in elective GS.

KEYWORDS

carrier, clonal hematopoiesis of indeterminate potential, elective genome, pharmacogenetics

1 | INTRODUCTION

Genome sequencing (GS) has entered clinical practice as an efficient approach to the diagnosis of rare genetic disorders (Bick et al., 2019). However, interest in this testing is not limited to patients with a medical indication for testing. Individuals without a medical indication request a variety of genetic tests, including GS. Such testing is referred to as "elective" genetic and genomic testing (https://en.wikipedia.org/wiki/Elective_genetic_and_genomic_testing; Lu et al., 2019).

Elective testing uses GS or exome sequencing (ES) to evaluate an individual for both primary findings and secondary findings. Primary findings include variants that purport to explain an aspect of the patient's medical or family history. Secondary findings are variants that do not appear to be associated with medical or family history at the time of testing but are nevertheless clinically relevant. Examples of

TABLE 1 Variants reported by elective clinical genome sequencing.

Participant information				Variant information	
Insight number	**Age**	**Sex**	**ICD10**	**Variant category**	**Gene**
1	55	F	Oth Disorders Of Plasma-Protein Metabolism, Nec E88.09 Sleep Apnea, Unspecified G47.30 Restless Legs Syndrome G25.81 Dysthymic Disorder F34.1	Pharmacogenetic Secondary Carrier	BCHE CNGB3
2	69	F	Giant Cell Arteritis With Polymyalgia Rheumatica M31.5	Secondary Carrier Secondary Carrier Secondary Carrier	BBS1 RNASEH2B TACR3
3	51	F	Hypothyroidism, Unspecified E03.9	no reportable variants identified	
4	32	F	Attention-Deficit Hyperactivity Disorder, Unspecified Type F90.9	Secondary Carrier	PCDH15
5	63	F	Eosinophilic Esophagitis K20.0 Dysthymic Disorder F34.1	Secondary Carrier Secondary Carrier Secondary Disease	GCDH CLCN1 ASB10
6	73	F	Parkinson's Disease G20 Abnormal Weight Loss R63.4 Unspecified Age-Related Cataract H25.9 Unspecified Sensorineural Hearing Loss H90.5 Unspecified Dementia Without Behavioral Disturbance F03.90	no reportable variants identified	
7	74	M	Malignant Neoplasm Of Prostate C61 Low Back Pain M54.5 Unspecified Atrial Fibrillation I48.91 Dvrtclos Of Lg Int W/o Perforation Or Abscess W Bleeding K57.31 Unspecified Abdominal Hernia Without Obstruction Or Gangrene K46.9 Gilbert Syndrome E80.4 Polyp Of Colon K63.5 Cortical Age-Related Cataract, Unspecified Eye H25.019 Endothelial Corneal Dystrophy H18.51	Primary Secondary Carrier	MSR1 SERPIN A1
8	59	F	Exercise Induced Bronchospasm J45.990 Celiac Disease K90.0	Secondary Carrier	GPSM2
9	81	M	Malignant Neoplasm Of Prostate C61 Unspecified Sensorineural Hearing Loss H90.5 Unspecified Cataract H26.9 Frequency Of Micturition R35.0	Primary Secondary Carrier Secondary Carrier	MSR1 SLC45A 2 GALC
10	79	M	Age-Related Cognitive Decline R41.81 Unspecified Age-Related Cataract H25.9 Low Back Pain M54.5 Pain In Unspecified Hip M25.559 Other Chronic Sinusitis J32.8	no reportable variants identified	
11	57	F	Syncope And Collapse R55 Renal Agenesis, Unilateral Q60.0 Congenital Absence Of Ovary, Unilateral Q50.01	Primary	NKX2-5 NM_00116617
12	59	M	Old Myocardial Infarction I25.2 Tinea Unguium B35.1 Other Intervertebral Disc Displacement, Lumbar Region M51.26 Sleep Apnea, Unspecified G47.30 Hyperlipidemia, Unspecified E78.5 Essential (primary) Hypertension I10 Polyp Of Colon K63.5	Secondary Carrier Secondary Carrier	HFE GAA

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_024006.5	chr3:g.165547569G>T	1253G>T	NA	NA
NM_019098	chr8:g.87656009delG	1148delC	T383Ifs*13	Pathogenic
NM_024649	chr11:g.66293652T>G	1169T>G	M390R	Pathogenic
NM_024570	chr13:g.51519581G>A	529G>A	A177T	Pathogenic
NM_001059	chr4:g.104577415C>T	824G>A	W275*	Likely Pathogenic
NM_001142768	chr10:g.55698574C>T	NA	NA	Pathogenic
NM_000159	chr19:g.13010300C>T	1262C>T	A421V	Pathogenic
NM_000083	chr7:g.143048771C>T	2680C>T	R894*	Pathogenic
NM_001142460	chr7:g.150884003C>T	215G>A	R72H	Pathogenic
NM_138715	chr8:g.16012590C>T	881G>A	G294E	VUS
NM_001002236	chr14:g.94844947C>T	1096G>A	E366K	Pathogenic
NM_013296	chr1:g.109466682C>A	1661C>A	S554*	Likely Pathogenic
NM_138715	chr8:g.16012590C>T	881G>A	G294E	VUS
NM_001012509	chr5:g.33951658C>G	NA	NA	Likely Pathogenic
NM_000153	chr14:g.88452941T>C	334A>G	T112A	Likely Pathogenic
	chr5:g.172660374C>T	428G>A	R143Q	VUS
NM_000410	chr6:g.26093141G>A	845G>A	C282Y	Pathogenic
NM_000152	chr17:g.78078341T>G	NA	NA	Pathogenic

(Continues)

TABLE 1 (Continued)

Participant information				Variant information	
Insight number	Age	Sex	ICD10	Variant category	Gene
13	57	F	Oth Types Of Non-Hodg Lymph, Nodes Of Head, Face, And Neck C85.81 Hyperlipidemia, Unspecified E78.5 Hypothyroidism, Unspecified E03.9 Acute Embolism And Thrombosis Of Other Thoracic Veins I82.290	Primary Primary Secondary Carrier Secondary Carrier Secondary Carrier	F5 PRF1 SERPIN A1 MVK TMPRSS3
14	53	M	Chronic Ischemic Heart Disease, Unspecified I25.9 Essential (primary) Hypertension I10 Hyperlipidemia, Unspecified E78.5 Gastro-Esophageal Reflux Disease Without Esophagitis K21.9 Anodontia K00.0	Primary Secondary Carrier Secondary Carrier Secondary Carrier	WNT10A PYGM TYR ATM
15	31	M	Acne Vulgaris L70.0 Mild Intermittent Asthma, Uncomplicated J45.20 Tension-Type Headache, Unspecified, Not Intractable G44.209	Pharmacogenetic Pharmacogenetic Pharmacogenetic	TPMT TPMT NUDT15
16	61	M	Gastro-Esophageal Reflux Disease Without Esophagitis K21.9 Essential (primary) Hypertension I10 Obstructive Sleep Apnea (adult) (pediatric) G47.33	Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	ACADM C5orf42 COL4A3 JAGN1 WDR72
17	34	F	Anxiety Disorder, Unspecified F41.9 Hypothyroidism, Unspecified E03.9 Attention-Deficit Hyperactivity Disorder, Unspecified Type F90.9	no reportable variants identified	
18	51	M	Pure Hypercholesterolemia, Unspecified E78.00 Essential (primary) Hypertension I10 Disorder Of Bilirubin Metabolism, Unspecified E80.7 Allergy To Peanuts Z91.010	Secondary Carrier Secondary Carrier	MTFMT SERPINA1
19	35	F	Calculus Of Kidney N20.0	Primary Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	CYP24A1 HFE RNASEH2B SLC26A3 WRAP53
20	49	M	Essential (primary) Hypertension I10	Secondary Carrier Secondary Carrier Secondary Carrier	FGB IDUA TG
21	44	F	Eclampsia Complicating The Puerperium O15.2 Malignant Neoplasm Of Unsp Site Of Unspecified Female Breast C50.919 Supraventricular Tachycardia I47.1	Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	AGXT CBS DHCR7 G6PD
22	46	M	Neoplasm Of Uncertain Behavior Of Connctv/soft Tiss D48.1	no reportable variants identified	
23	63	M	Persistent Atrial Fibrillation I48.1 Noise Effects On Left Inner Ear H83.3X2	Secondary Carrier Secondary Disease	CYP17A1 WNT10A

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_000130	chr1:g.169519049T>C	1601A>G	Q534R	Pathogenic
NM_001083116	chr10:g.72357895delG	1582delC	H528Tfs*85	Likely Pathogenic
NM_001127701	chr14:g.94847262T>A	863A>T	E288V	Pathogenic
NM_000431	chr12:g.110024570C>T	643C>T	R215*	Pathogenic
NM_024022	chr21:g.43795896C>T	1276G>A	A426T	Likely Pathogenic
NM_025216	chr2:g.219755011T>A	682T>A	F228I	Pathogenic
NM_001164716	chr11:g.64527223G>A	148C>T	R50*	Pathogenic
NM_000372	chr11:g.89017973C>T	1217C>T	P406L	Pathogenic
NM_000051	chr11:g.108121753_108 121754delAG	1561_1562delAG	E522Ifs*43	Pathogenic
NM_000367.3	chr6:g.18130918T>C	c.719A>G	NA	NA
NM_000367.3	chr6:g. 18139228C>T	c.460G>A	NA	NA
NM_018283.3	chr13:g.48619855C>T	c.415C>T	NA	NA
NM_000016.5	chr1:g. 76226846A>G	c.985A>G	p.Lys329Glu	Pathogenic
NM_023073.3	chr5:g. 37226878delA	c.1819delT	p.Tyr607ThrfsTer6	Likely Pathogenic
NM_000091.4	chr2:g. 228176554C>T	c.4981C>T	p.Arg1661Cys	Likely Pathogenic
NM_032492.3	chr3:g. 9932409G>A	c.3G>A	p.Met1?	Pathogenic
NM_182758.3	chr15:g. 54003546G>A	c.844C>T	p.Gln282Ter	Likely Pathogenic
NM_139242.3	chr15:g. 65313871G>A	c.626C>T	p.Ser209Leu	Pathogenic
NM_000295.4	chr14:g. 94847262T>A	c.863A>T	p.Glu288Val	Likely Pathogenic
NM_000782.4	chr20:g. 52788190G>A	c.469C>T	p.Arg157Trp	VUS
NM_000410.3	chr6:g.26093141G>A	c.845G>A	p.Cys282Tyr	Pathogenic
NM_024570.3	chr13:g.51519581G>A	c.529G>A	p.Ala177Thr	Pathogenic
NM_000111.2	chr7:g. 107412534_1074 12535insTGA	c.2026_2027dupTCA	p.Ile675dup	Likely Pathogenic
NM_018081.2	chr17:g. 7591983_75919 84delCT	c.17_18delCT	p.Gln7ThrfsTer27	Likely Pathogenic
NM_005141.4	chr4:g. 155486984C>T	c.139C>T	p.Arg47Ter	Pathogenic
NM_000203.4	chr4:g. 996535G>A	c.1205G>A	p.Trp402Ter	Pathogenic
NM_003235.4	chr8:g. 133894854C>T	c.886C>T	p. Arg296Ter	Pathogenic
NM_000030.2	chr2:g. 241808773C>T	c.352C>T	p.p.Arg118Cys	Likely Pathogenic
NM_000071.2	chr21:g. 44478972C>T	c.1330G>A	p. Asp444Asn	Likely Pathogenic
NM_001360.2	chr11:g. 71146886C>G	c.964-1G>C	NA	Pathogenic
NM_000402.4	chrX:g. 153760649C>G	c.1406G>C	p.Arg469Pro	Likely Pathogenic
NM_000102.3	chr10:g. 104596941_104 596942insT	c.177dupA	p.Tyr60IlefsTer29	Likely Pathogenic
NM_025216.2	chr2:g. 219755011T>A	c.682T>A	p.Phe228Ile	Pathogenic

(Continues)

TABLE 1 (Continued)

Participant information				Variant information	
Insight number	Age	Sex	ICD10	Variant category	Gene
24	74	M	Rheumatoid arthritis M05.89 Onychomycosis B35.1 Gallstones K80.0 Kidney stones N20.0	Primary Secondary Carrier Secondary Carrier Pharmacogenetic Pharmacogenetic Pharmacogenetic Pharmacogenetic Pharmacogenetic	CLEC7A GAA USH2A TMPT*3A TMPT*3A CYP2D6*6 CYP2C19*17 UGT1A1*80
25	71	F	Major Depressive Disorder F33.9 Interstitial Pulmonary Disease J84.9	Secondary Carrier	MED25
26	59	M	Paroxysmal Atrial Fibrillation I48.0 Essential Hypertension I10 Behign Neoplasm of Cerebral Meninges D32.0	Secondary Disease	WNT10A
27	62	M	Benign prostatic hypertrophy N40.1 Age-related cognitive decline R41.84	Secondary Disease Secondary Carrier Secondary Carrier Pharmacogenetic Pharmacogenetic Pharmacogenetic	APOC3 GJB2 LOXHD1 CYP2C19 SLCO1B1 VKORC1
28	71	F	Other Specified Forms of Tremor G25.2 Abnormal Head Movements R25.0 Unspecified Voice and Resonance Disorder R49.9 Other Chorea G25.5 Hypothyroidism, Unspecified E03.9 Other Age-Related Cataract H25.89 Other Muscle Spasm M628.38	Secondary Carrier	TYR
29	70	F	Malignant Neoplasm of Breast C50.919 Family History of Epilepsy and Other Disease of the Nervous System Z82.0	Primary Primary Secondary Carrier Secondary Carrier	PER3 PER3 SERPINA1 SLC7A9
30	69	F	Primary Osteoarthritis, Right Hand M19.041 Primary Osteoarthritis, Left Hand 19.042 Pure Hypercholesterolemia E78.00 Sensorineural HL, Ulilateral H90.42 Cyclical Vomiting, Not Intractable G43.A0	Secondary Carrier Secondary Carrier	RSPH1 TACR3
31	61	M	Pure Hypercholesterolemia, Unspecified E78.00 Essential (primary) Hypertension I10	Secondary Carrier Secondary Carrier Secondary Disease Secondary Carrier Secondary Carrier Secondary Carrier	ACADM EVC2 SLC3A1 USH2A ALG12 COL9A1

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_197947	chr12:g.10271087A>C	714T>G	Y238*	VUS
NM_001079804	chr17:g.78078341T>G	NA	NA	Pathogenic
NM_007123	chr1:g.216497582C>A	1256G>T	C419F	Pathogenic
NM_000367.3	chr6:18130918A>G	c.719A>G	NA	NA
NM_000367.3	chr6:1139228G>A	c.460G>A	NA	NA
NM_000769.2	chr22:42525086delT	c. 454delT	NA	NA
NM_000769.2	chr10:96521657C>T	c.−806C>T	NA	NA
NM_019075.2	chr2:234668570C>T	c.−364C>T	NA	NA
NM_030973.3	chr19:g. 50334047C>T	c.1004C>T	p.Ala335Val	Likely Pathogenic
NM_025216.2	chr2:g. 219755011T>A	c.682T>A	p.Phe228Ile	Likely Pathogenic
NM_000040.1	chr11:g. 116701354G>A	c.55+1G>A	NA	Pathogenic
NM_004004.5	chr13:g. 20763686delC	c.35delG	p.Gly12ValfsTer2	Pathogenic
NM_144612.6	chr18:g. 44109190G>A	c.4480C>T	p.Arg1494Ter	Pathogenic
NM_000769.2	chr10:g.96541616G>A	c.19154G>A	NA	NA
NM_006446.4	chr12:g.21331549T>C	c.521T>C	NA	NA
NM_024006. 5	chr16:g.31107689C>T	c.−1639G>A	NA	NA
NM_000372.4	chr11:g. 89018126A>G	c.1366+4A>G	NA	Likely Pathogenic
NM_001289862.1	chr1:g. 7869953C>G	c.1243C>G	p.Pro415Ala	VUS
NM_001289862.1	chr1:g. 7869960A>G	c.1250A>G	p.His417Arg	VUS
NM_000295.4	chr14:g. 94844947C>T	c.1096G>A	p.Glu366Lys	Pathogenic
NM_014270.4	chr19:g. 33353427C>T	c.544G>A	p.Ala182Thr	Pathogenic
NM_080860.3	chr21:g. 43906573T>G	c.275-2A>C	NA	Pathogenic
NM_001059.2	chr4:g. 104577415C>T	c.824G>A	p.Trp275Ter	Pathogenic
NM_000016.5	chr1:g.76226846A>G	c.985A>G	p.Lys329Glu	Pathogenic
NM_147127.4	chr4:g.5633522G>A	c.1708C>T	p.Gln570Ter	Pathogenic
NM_000341.3	chr2:g.44539839G>T	c.1447G>T	p.Glu483Ter	Pathogenic
NM_007123.5	chr1:g. 216363622_216363623delAG	c.4338_4339delCT	p.Cys1447GlnfsTer29	Pathogenic
NM_024105.3	chr22:g.50307032C>T	c.295+1G>A	NA	Likely Pathogenic
NM_001851.4	chr6:g.70981381C>A	c.1120G>T	p.Glu374Ter	Likely Pathogenic

(Continues)

TABLE 1 (Continued)

Participant information				Variant information	
Insight number	Age	Sex	ICD10	Variant category	Gene
32	55	F	Tic Disorder, Unspecified F95.9 Rosacea, Unspecified L71.9 Dry Eye Syndrome H04.129 Cerv Disc Disord M50.020 Raynaud's Syndrome I73.00 Hypothyroidism, Unspecified E03.9 Polyp of Colon K63.5 MIgraine G43.909	Primary Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	MSH2 AIRE CFTR DMP1 FANCA MYBPC1
33	67	M	Hyperlipidemia, Unspecified E78.5 Circadial Rhythm Sleep Disord G47.20 Unspecified Hearing Loss H91.90	Primary Secondary Disease Secondary Carrier	LIPI APC TUBGCP4
34	67	F	Hyperlipidemia, Unspecified E78.5 Episodic Cluster Headache G44.019 Essential (primary) Hypertension I10	Secondary Carrier	MEFV
35	30	M	Anxiety Disorder, Unspecified F41.9 Attention-Deficit Hyperactivity Disorder, Other Type F90.8	Secondary Carrier Secondary Carrier	LIG4 NAGA
36	74	M	Polyneuropathy, unspecified G62.9 Essential Tremor G25.0 Malignant Neoplasm of Prostate C61 Unspecified Sensorineural Hearing Loss H90.5 Other Seborrheic Keratosis L82.1	Primary Primary Secondary Carrier Secondary Carrier	COL11A2 SPTLC2 SERPINA1 CEP104
37	68	F	Malignant Neoplasm Of Unspecified Site Of Left Female Breast C50.912 Transient Cerebral Ischemic Attack, Unspecified G45.9 Supraventricular Tachycardia I47.1 Mild Persistent Asthma, Uncomplicated J45.30 Unspecified Osteoarthritis, Unspecified Site M19.90 Gastro-Esophageal Reflux Disease Without Esophagitis K21.9 Essential (primary) Hypertension I10 Raynaud's Syndrome Without Gangrene I73.00 Rosacea, Unspecified L71.9 Acquired Absence Of Other Specified Parts Of Digestive Tract Z90.49 Dvrtclos Of Lg Int W/o Perforation Or Abscess W/o Bleeding K57.30	Primary Secondary Carrier	COL6A3 ACADM
38	63	M	Headache R51 Hyperlipidemia, Unspecified E78.5 VentricularPrematureDepolarization!49.3 Other Specified Anxiety Disorders F41.8 GERD K21.0 Gout, Unspecified M10.9 Mycosis Fungoides, Unspecified Site C84.00 Obstructive Sleep Apnea G47.33 Type 2 DM without Complications E11.9 Osteoarthritis M19.90	Primary Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	TET2 GJB2 PKLR SLC6A19 USH2A

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_000251.2	chr:2g.47637301T>G	c.435T>G	p.Ile145Met	VUS
NM_000383	chr21:g.45711063_45711075delGCCTGTCCCCTCC	c.965_977delGCCTGTCCCCTCC	p.Leu323SerfsTer51	Pathogenic
NM_000492.3	chr7:g.117199645_11719964delTCT	c.1520_1522delTCT	p.Phe508del	Pathogenic
NM_004407.3	chr4:g.88578228G>A	c.99G>A	p.Trp33Ter	Pathogenic
NM_000135.2	chr16:g.89828378_89828379insCAGCTTCAGGTTGAATTTC	c.2830_2831dupGAAATTCAACCTGAAGCTG	p.Asp944GlyfsTer5	Pathogenic
NM_002465.3	chr12:g.102071879G>A	c.3110-1G>A	NA	Likely Pathogenic
NM_198996.3	chr21:g. 15561623C>T	c.227G>A	p.Cys76Tyr	VUS
NM_000038.5	chr5:g. 112175211T>A	c.3920T>A	p.Ile1307Lys	Likely Pathogenic
NM_014444.4	chr15:g. 43675557_4367 5558insT	c.578insT	p.Gly194TrpfsTer8	Likely Pathogenic
NM_000243.2	chr16:g. 3293257C>A	c.2230G>T	p.Ala744Ser	Likely Pathogenic
NM_002312.3	chr13:g.108862342_108862346delTCTTT	c.1271_1275delAAAGA	p.Lys424ArgfsTer20	Pathogenic
NM_000262.2	chr22:g.42457056C>T	c.973G>A	p.Glu325Lys	Likely Pathogenic
NM_080679.2	chr6:g.33141822C>T	c.2174G>A	p.Gly725Glu	VUS
NM_004863.3	chr14:g.78045365A>G	c.415T>C	p.Cys139Arg	VUS
NM_000295.4	chr14:g.94844947C>T	c.1096G>A	p.Glu366Lys	Pathogenic
NM_014704.3	chr1:g.3750458delG	c.1627delC	p.Arg543AlafsTer33	Likely Pathogenic
NM_004369.3	chr2:g.238243533C>G	c.8966-1G>C	NA	Pathogenic
NM_000016.5	chr1:g.76226846A>G	c.985A>G	p.Lys329Glu	Pathogenic
NM_001127208.2	chr4:g.106182914A>C	c.3955-2A>C	NA	Likely Pathogenic
NM_004004.5	chr13:g.20763744T>G	c.−22-2A>C	NA	Pathogenic
NM_000298.5	chr1:g.155261709G>A	c.517G>A	p.Asp173Asn	Pathogenic
NM_001003841.2	chr5:g.1212453G>A	c.517G>A	p.Asp173Asn	Pathogenic
NM_007123.5	chr1:g.216595590A>T	c.89T>A	p.Leu30Ter	Likely Pathogenic

(Continues)

TABLE 1 (Continued)

Participant information				Variant information	
Insight number	Age	Sex	ICD10	Variant category	Gene
39	62	F	Fibromyalgia M79.7 Primary Hypertension I10 Hyperlipidemia E78.5 Unspecified Osteoarthritis M19.90 GERD K21.0	Secondary Carrier Secondary Carrier Secondary Disease	COL18A1 VWF WNT10A
40	89	F	Idiopathic Pulmonary Fibrosis J84.112 Hyperlipidemia E78.5 Unspecified Osteoarthritis M19.90 Age-Related Cataract H25.9	Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	ATP7B GJB2 PKLR SLC6A19 USH2A
41	34	M	Rhabdomyolysis M62.82 Hemochromatosis E83.119 Abnormal Levels of Other Serum Enzymes R74.8 Pure Hypercholesterolemia E78.00	Primary Primary Secondary Carrier Secondary Carrier	ANO5 HFE IDUA STARD9
42	88	M	Unspecified Hearing Loss H91.90 Angina Pectoris I20.9 Prediabetes R73.03 Macular Degeneration H35.30 Age-Related Cataract H25.9 Unspecified Osteoarthritis M19.90 Family History of Carrier of Other Genetic Disease Z84.81	Primary Primary Primary Primary Primary Secondary Carrier Secondary Carrier	ABCA4 CDH23 HMCN1 THAP1 THAP1 FANCA SERPINA1
43	72	M	Parkinson's Disease G20 Persistant Atril Fibrillation I48.1 Other Age-Related Cataract H25.89	Secondary Disease Secondary Carrier Secondary Carrier Secondary Disease Secondary Carrier	BRCA2 HFE MCPH1 NLRP3 GNRHR
44	52	M	Hyperlipidemia, Unspecified E78.5 Gout, Unspecified M10.9 Obstructive Sleep Apnea G47.33	Primary Secondary Carrier Secondary Carrier Secondary Carrier Pharmacogenetic Pharmacogenetic Pharmacogenetic Pharmacogenetic	STAP1 OCA2 ADAR PNPO CYP2C9 VKORC1 CYP2C19 CYP2D6
45	72	M	Rheumatoid Arthritis, Unspecified M06.9 Calculus Of Kidney N20.0 Malignant Melanoma Of Skin, Unspecified C43.9 Unspecified Age-Related Cataract H25.9 Acute Myocardial Infarction, Unspecified I21.9	Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	BCHE FKBP14 IRAK4 LIPA FLG2 IL17RA PEX6

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_030582.3	chr21:g.46911182_46911183insC	c.2651insC	p.Gly887ArgfsTer23	Pathogenic
NM_000552.4	chr12:g.6143978C>T	c.2561G>A	p.Arg854Gln	Pathogenic
NM_025216.2	chr2:g.219755011T>A	c.682T>A	p.Phe228Ile	Likely Pathogenic
NM_000053.3	chr13:g.52518281G>T	c.3207C>A	p.His1069Gln	Pathogenic
NM_004004.5	chr13:g.20763744T>G	c.−22-2A>C	NA	Pathogenic
NM_001003841.2	chr1:g.155261709G>A	c.517G>A	p.Arg486Trp	Pathogenic
NM_001003841.2	chr5:g.1212453G>A	c.517G>A	p.Asp173Asn	Pathogenic
NM_007123.5	chr1:g.216595590A>T	c.89T>A	p.Leu30Ter	Likely Pathogenic
NM_213599.2	chr11:g.22242646_22242647insA	c.184insA	p.Asn64LysfsTer15	Pathogenic
NM_000410.3	chr6:g.26093141G>A	c.845G>A	p.Cys282Tyr	Pathogenic
NM_000203.4	chr4:g.981646C>T	c.208C>T	p.Gln70Ter	Pathogenic
NM_020759.2	chr15:g.42987963T>A	c.13169T>A	p.Leu4390Ter	Likely Pathogenic
NM_000350.2	chr1:94508969G>A	c.3113C>T	p.Ala1038Val	Pathogenic
NM_022124.5	chr10:73491873A>G	c.3845A>G	p.Asn1282Ser	VUS
NM_031935.2	chr1:186143745G>A	c.15914G>A	p.Arg5305Gln	VUS
NM_018105.2	chr8:42694447T>C	c.149A>G	p.Tyr50Cys	VUS
NM_018105.2	chr8:42694435C>G	c.161G>C	p.Cyc54Ser	VUS
NM_000135.2	chr16:89816189C>T	c.3188G>A	p.Trp1063Ter	Pathogenic
NM_0002095.4	chr14:94847262T>A	c.863A>T	p.Glu288Val	Pathogenic
NM_000059.3	chr13:32913457C>G	c.4965C>G	p.Try1655Ter	Pathogenic
NM_000410.3	chr6:26093141G>A	c.845G>A	p.Cys282Tyr	Pathogenic
NM_024596.4	chr8:6296599_6296600insA	c.562insA	p.Asn189LysfsTer15	Pathogenic
NM_004895.4	chr1:247587343G>A	c.598G>A	p.Val200Met	Pathogenic
NM_000406.2	chr4:68606400C>T	c.785G>A	p.Arg262Gln	Likely Pathogenic
NM_012108	chr4:g.68424562G>A	35G>A	R12H	VUS
NM_000275	chr15:g.28230247C>T	1327G>A	V443I	Pathogenic
NM_015840	chr1:g.154574541G>C	577C>G	P193A	Pathogenic
NM_018129	chr17:g.46019139A>T	98A>T	D33V	Pathogenic
NM_000771.3	chr10:96702047C>T	c.430C>T	NA	NA
NM_024006.5	chr16:31107689-1639G>A	c.−1639G>A	NA	NA
NM_000769.2	chr10:96521657-806C>T	c.−806C>T	NA	NA
NM_000106.5	chr22:425338052988G>A	c.2988G>A	NA	NA
NM_000055.3	chr3:165548529T>C	c.293A>G	p.Asp98Gly	Pathogenic
NM_017946.3	chr7:30058726_3005 8727insG	c.362dupC	p.Glu122ArgfsTer7	Pathogenic
NM_016123.3	chr12:44176108A>G	c.942-2A>G	NA	Pathogenic
NM_000235.3	chr10:90982268C>T	c.894G>A	p.Gln298Gln	Pathogenic
NM_001014342.2	chr1:152326321_152 326322insTA	c.3940_3941dupTA	p.Thr1314IlefsTer223	Likely Pathogenic
NM_014339.6	chr22:17566012_175 66013insT	c.31insT	p.Pro14AlafsTer42	Likely Pathogenic
NM_000287.3	chr6:42935188C>T	c.1802G>A	p.Arg601Gln	Likely Pathogenic

(Continues)

TABLE 1 (Continued)

Participant information				Variant information	
Insight number	**Age**	**Sex**	**ICD10**	**Variant category**	**Gene**
46	56	F	Ulcerative (chronic) Proctitis Without Complications K51.20 Pure Hypercholesterolemia, Unspecified E78.00 Psoriasis, Unspecified L40.9 Other Specified Congenital Deformities Of Feet Q66.89	Secondary Carrier Secondary Carrier Secondary Disease Secondary Carrier	HFE TUBGCP4 VKORC1 CTC1
47	58	F	Endometriosis Of Pelvic Peritoneum N80.3 Crohn's Disease, Unspecified, Without Complications K50.90 Personal History Of Urinary Calculi Z87.442 Cervicalgia M54.2	Secondary Carrier Secondary Carrier Secondary Carrier Secondary Carrier	ABCA4 ABCC6 DNAH17 GALT
48	71	M	Major Depressive Disorder, Recurrent, Mild F33.0 Gout, Unspecified M10.9 Athscl Heart Disease Of Native Coronary Artery W/o Ang Pctrs I25.10 Unspecified Atrial Flutter I48.92 Unspecified Age-Related Cataract H25.9 Tinnitus, Bilateral H93.13	Secondary Carrier Secondary Disease Secondary Carrier	AURKC APC SUN5
49	65	F	Breast cancer C50.919 Mixed hyperlipidemia E78.2 Cortical age-related cataract H25.013 Other disturbance of skin sensation R20.8	Secondary Carrier Secondary Carrier	DPYD LIPE
50	65	M	Type 2 Diabetes E11.9 Cortical age-related cataract H25.013 Mixed hyperlipidemia E78.2 Palmar fascial fibromatosis M72.0 Benign paroxysmal vertigo H81.10	Primary Secondary Carrier Secondary Carrier Secondary Carrier Secondary Disease	LPL BBS10 PIGO ROM1 WNT10A
51	66	F	Selective Deficiency Of Immunoglobulin A [iga] D80.2 Autoimmune Thyroiditis E06.3 Inflammatory Polyarthropathy M06.4	Secondary Carrier Secondary Carrier Secondary Carrier	GCDH DHTKD1 SEC24D
52	77	M	Hereditary And Idiopathic Neuropathy, Unspecified G60.9	Primary Secondary Carrier Secondary Carrier Secondary Disease Secondary Carrier	NOD2 GDF1 MAN2B1 ASXL1 MMP21

Variant classification in the table reflects the classification at the time of analysis and reporting. These classifications may have changed since the analysis and reporting of these genomes to participants.

secondary findings include a pathogenic *BRCA1 (*113705)* variant in an individual with no known personal or family history of breast/ovarian cancer and carrier status for an autosomal recessive condition for which there is no known family history.

The frequency and nature of the primary and secondary findings reported in elective genome studies have been quite variable for a number of reasons (Table A1). Patient recruitment criteria were not uniform across studies. For example, all study subjects were provided testing for free as part of a research project except those reported by Hou et al. (2020). In addition, the list of genes analyzed and criteria used for variant classification varied across studies. Since the first papers describing the use of elective genomic testing were published in 2012, the knowledge base concerning the association between genetic variants and human disease has grown significantly with the development of resources such as ClinVar, ClinGen, and gnomAD. As a result, recent elective testing produces more clinically relevant findings than did earlier testing. Further, while all elective GS and ES studies correlated variants with medical history, family history was not always considered. Some participants were likely motivated

Transcript	Variant (genomic)	Variant (coding)	Variant (protein)	Variant classification
NM_000410.3	chr6:26091179C>G	c.187C>G	p.His63Asp	Pathogenic
NM_014444.4	chr15:43675557_436 75558insT	c.578insT	p.Gly194TrpfsTer8	Pathogenic
NM_024006.5	chr16:31105945C>A	c.106G>T	p.Asp36Tyr	Pathogenic
NM_025099.5	chr17:8133261G>A	c.2959C>T	p.Arg987Trp	Likely Pathogenic
NM_000350.3	chr1:94008251C>T	c.5882G>A	p.Gly1961Glu	Pathogenic
NM_001171.5	chr16:16208798C>A	c.724G>T	p.Glu242Ter	Pathogenic
NM_173628.3	chr17:78552801_785 52802delTT	c.2182_2183delAA	p.Lys728AspfsTer19	Likely Pathogenic
NM_000155.3	chr9:34646576_3464 6579delCAGT	c.−116-3_−116delGTCA	NA	Likely Pathogenic
NM_001015878.1	chr19:57232070delC	c.145delC	p.Leu49TrpfsTer23	Pathogenic
NM_000038.6	chr5:112839514T>A	c.3920T>A	p.Ile1307Lys	Risk Variant
NM_080675.4	chr20:32985140G>A	c.943C>T	p.Gln315Ter	Likely Pathogenic
NM_000110.3	chr1:97828127G>A	c.220C>T	p.Arg74Ter	Likely Pathogenic
NM_005357.4	chr19:42402869delC	c.2705delG	p.Ser902ThrfsTer27	Likely Pathogenic
NM_000237.3	chr8:19956018A>G	c.953A>G	p.Asn318Ser	Pathogenic
NM_024685.4	chr12:76347713_763 47714insA	c.271dupT	p.Cys91LeufsTer5	Pathogenic
NM_032634.3 I	chr9:35092076_3509 2077insG	c.1810dupC	p.Arg604ProfsTer40	Pathogenic
NM_000327.3	chr11:62613611_626 13612insG	c.339dupG	p.Leu114AlafsTer18	Likely Pathogenic
NM_025216.3	chr2:218890289T>A	c.682T>A	p.Phe228Ile	Likely Pathogenic
NM_000159.4	chr19:12896249G>C	c.680G>C	p.Arg227Pro	Pathogenic
NM_018706.7	chr10:12112930G>A	c.2185G>A	p.Gly729Arg	Likely Pathogenic
NM_014822.4	chr4:118797796G>A	c.928C>T	p.Arg310Ter	Likely Pathogenic
NM_022162.2	chr16:50712015C>T	c.2104C>T	p.Arg702Trp	Risk Variant
NM_001492.5	chr19:18869035G>T	c.681C>A	p.Cys227Ter	Pathogenic
NM_000528.4	chr19:12657482G>T	c.1383C>A	p.Tyr461Ter	Pathogenic
NM_015338.5	chr20:32433747C>T	c.1549C>T	p.Gln517Ter	Likely Pathogenic
NM_147191.1	chr10:125767530A>T	c.1410+2T>A	NA	Likely Pathogenic

to undertake elective testing due to a suspected genetic disorder in the family. Considering these factors, it is unsurprising that studies examining patient perceptions and economic aspects of elective genomic testing yield a range of results and recommendations (Baptista et al., 2016; East et al., 2019; Fiala et al., 2019; Flemin et al., 2019; Lewis et al., 2016; Lupo et al., 2016; Price et al., 2017; Roberts et al., 2018; Sanderson et al., 2016; Zoltick et al., 2019).

More research is needed to explore the clinical and personal impact of elective GS, across different clinical contexts and patient populations. In an effort to understand how elective GS can be integrated into routine clinical genetics practice, we evaluated a patient population that underwent elective GS on a self-pay basis.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the Western Institutional Review Board (WIRB #20161118).

2.2 | Clinical evaluation and testing

Study recruitment occurred at the Smith Family Clinic for Genomic Medicine (SFC) located on the campus of HudsonAlpha Institute for Biotechnology in Huntsville, AL. Individuals became patients at the clinic either through consult requests from an outside provider or via self-referral. All patients who sought a clinic appointment specifically for elective genomic testing and were 18 years or older were eligible for this study. Additionally, a single patient who came to SFC for a diagnostic purpose (neuropathy) and decided to pursue elective genome sequencing *in addition to* the recommended genetic testing strategy was also eligible. All participants provided informed consent and institutional review board approval was obtained from the Western Institutional Review Board.

Prior to their in-clinic evaluation, individuals were invited to access an online patient communication and education tool, Genome Gateway. This tool allows patients to complete preliminary questionnaires and a pedigree and to receive both general and targeted educational materials. Clinical evaluation of participants included a thorough gathering of medical and family history, review of previous medical records, and a physical exam. Participants received pre-test genetic counseling regarding potential outcomes and result types, benefits, and limitations of testing, and considerations for testing, including the limits of current knowledge and familial and insurance implications of results.

Individuals were counseled that their results would include primary findings related to a known personal or family history of disease and could include secondary findings unrelated to a known history but still medically significant if requested. The GS laboratory reports potential secondary findings in the following categories: untreatable childhood diseases (e.g., Tay-Sachs), treatable adult-onset diseases (e.g., Lynch syndrome), untreatable adult-onset diseases (e.g., Autosomal Dominant Alzheimer's Disease), carrier status for a genetic disorder, and a limited number of pharmacogenetic variants. Individuals opted into the categories of secondary results that they wished to receive.

As part of standard clinical practice, clinical whole-genome sequencing was performed to 40X coverage by the HudsonAlpha Clinical Services Lab, LLC using the HiSeq (Illumina) or NovaSeq 6000 (Illumina) platform. Secondary analysis of FASTQ files to generate variant call file (VCF) files was performed using GATK (https://gatk.broadinstitute.org/hc/en-us) or DRAGEN Bio-IT platform (Illumina). The VCF file was loaded into a proprietary variant annotation software platform, Carpe Novo (Worthey, 2017) or Codicem (https://hudsonalpha.org/codicem). All primary variants were confirmed via Sanger sequencing. The majority of secondary variants and pharmacogenetic variants were confirmed via Sanger sequencing. A machine learning method developed by Holt et al. (2021) allowed confidence in the accuracy of GS data without orthogonal confirmation for certain variants.

Variants were classified using the American College of Medical Genetics (ACMG) guidelines (Richards et al., 2016). Primary findings included pathogenic variants, likely pathogenic variants and variants of uncertain significance (VUSs). Secondary findings were limited to pathogenic and likely pathogenic variants in genes associated with Mendelian disorders. Selected pharmacogenetic variants were reported from the genome analysis.

Pharmacogenetic panel testing was performed by Kailos Genetics, Inc. using the MiSeq System (Illumina), with paired end 78 bp reads, to sequence selected variants within 42 pharmacogenetic genes. Kailos Genetics' PGxComplete™ panel was used to capture and enrich targeted regions of the genome, such that 98% of the resulting sequences were aligned to the target regions. Once sequenced, a proprietary cloud-based analysis system performed sample demultiplexing, quality assessment, alignment to the genome, variant calling, and report generation. As this pharmacogenetic test was a clinical product and enrollment occurred over a span of >4 years, the specific genes tested and variants reported evolved over time.

Patients received their clinical results and post-test genetic counseling via in-person appointment or conference call with a medical geneticist and genetic counselor. Prior to results disclosure, patients were queried about any changes to their results preferences, whether they had communicated with family members about their testing process, and whether they had any insurance concerns. A copy of the results was provided to patients as well as their referring physician, if requested by the patient.

3 | RESULTS

3.1 | Demographics and clinical evaluation

Fifty-two patients were eligible for the study and elected to enroll. The average age of participants was 61. There was a roughly even split between males and females, with 27 males and 25 females. Ninety-four percent ($n = 49$) of participants were primarily Caucasian, while four percent ($n = 2$) were Asian, and two percent ($n = 1$) were Latino. Forty-nine participants (94%) had at least a bachelor's degree, while 30 (58%) had an advanced degree. Common professions included physicians, lawyers, and executives.

An average of 76 minutes was spent on the pre-test clinical evaluation and counseling (range 24–161, median 75). Participants had an average of four ICD10 codes (range 1–11). Patients in the <50 years group had two ICD10 codes on average, while those in the 51–70 years group had four, and those in the >70 years group had five. Common

diagnoses included hyperlipidemia, age-related cataract, hypertension, and mild-moderate hearing loss. Seventeen participants (33%) reported undergoing prior genetic testing; the majority of these participants had undergone direct-to-consumer ancestry or health testing. Ninety percent ($n = 47$) of participants elected to receive all possible secondary findings, while the remaining 10% elected to receive all possible secondary results except for untreatable adult-onset conditions.

At the time of post-test counseling, all participants reported that they were satisfied with their current insurance coverage. None had changes in their preferences at the time of results disclosure. An average of 56 minutes was spent in post-test counseling and results discussion (range 30–102).

3.2 | Clinical genome sequencing results

Twenty-six primary results potentially related to clinical phenotype were identified in 18 of 52 participants (four individuals received multiple findings). This included 7 pathogenic variants, 2 likely pathogenic variants, 16 variants of uncertain significance, and 1 risk allele. No participants received secondary findings indicating an increased risk to develop an untreatable disease. Eight individuals (15%) received secondary findings related to treatable disease risk, three of these findings were in genes recommended for secondary disease analysis by the ACMG (Kalia et al., 2017) (two in *APC (*611731)*, and one in *BRCA2 (*600185)*). Eighty-five percent ($n = 44$) had a carrier status identified for at least one autosomal recessive or X-linked disorder (range 1–7 variants, median 2 variants). As part of the limited pharmacogenetic assessment of the genome, 16 variants were reported in five individuals. None of these variants impacted a current medication (Table 1).

3.3 | GS results compared to global screening array (GSA)

When compared to the variants found on the GSA (Illumina), 53% of all reported variants are represented on the array. This includes 43% of primary findings, 55% of secondary findings, and 60% of pharmacogenetic findings.

3.4 | Pharmacogenetics panel testing

Fifty-one (98%) elective GS patients underwent a separate stand-alone pharmacogenetics panel test. The pharmacogenetics panel test reported variants that alter drug metabolism and had the potential to impact a medication in all 51 (100%) patients. Twenty-one individuals (40%) had pharmacogenetic variants identified by this panel with the potential to impact a current medication (Table 2).

4 | DISCUSSION

4.1 | Primary findings

Our study found nine pathogenic or likely pathogenic variants that may explain one or more aspects of the medical history in six individuals (11.5%) who underwent elective genome sequencing. This is comparable to the results from a recently published elective genome program that found 11.5% (137/1,190) of participants had a genotype–phenotype association (Hou et al., 2020).

In four cases, primary findings included a single pathogenic or likely pathogenic variant in a gene associated with autosomal recessive disease that had some overlap with the patient's history. Case 13 had follicular lymphoma and was heterozygous for a c.1582delC frameshift variant in *PRF1 (*170280)*. Autosomal recessive *PRF1*-associated hemophagocytic lymphohistiocytosis may present with lymphoma as the initial manifestation (Tesi et al., 2016). Interestingly, there is evidence that carriers of *PRF1* variants are at risk for lymphomas (Chen et al., 2017; Ciambotti et al., 2014; Ding & Yang, 2013). Digenic inheritance has also been suggested (Clementi et al., 2004). Case 41 had an episode of severe rhabdomyolysis requiring an admission to the intensive care unit and was heterozygous for a c.191dupA frameshift variant in *ANO5 (*608662)*. While the second variant in *trans* was not identified, the patient's phenotype is consistent with the wide variability seen in *ANO5* muscle disease (Jarmula et al., 2019; Penttilä et al., 2012; Savarese et al., 2016). Reports suggest that carriers of *ANO5* variants may have a mild phenotype including cramps and increased CK (Jarmula et al., 2019; Savarese et al., 2016). Case 37 had episodic facial dystonia and was heterozygous for a c.8966-1G>C canonical splice site variant in *COL6A3 (*120250)*. The patient's phenotype resembles cases of autosomal recessive dystonia-27 (DYT-27), which is characterized by a slowly progressive phenotype that starts in the hand or neck and spares the lower extremities with a median age at onset of 22 years with a range of 6–61 years (Panda & Sharawat, 2020). The variant reported in case 37 was seen in two DYT-27 pedigrees (Jochim et al., 2016; Zech et al., 2015). Case 42 had age-related macular degeneration (AMD) and an established pathogenic *ABCA4 (*601691)* variant c.3113C>T (p. Ala1038Val). *ABCA4*-associated disease is a recessive disorder that ranges from early onset, rapidly progressing cone-rod dystrophy and retinitis pigmentosa to a very late-onset mild disease resembling AMD (Cremers et al., 2020; Zernant et al., 2017). In these cases, there are three potential explanations: (1) a second disease-causing variant is actually

TABLE 2 Selected pharmacogenetic variants reported by PGx Complete.

Insight number	Age	Sex	Gene	Genotype	Consequence
1	55	F	CYP2C9	*1/*2	Intermediate Metabolizer
2	69	F	IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
3	51	F	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP3A4	*1/*22	Reduced Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
4	32	F	IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C9	*2/*2	Poor Metabolizer
5	63	F	IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Met/Met	Reduced Stimulant Response
6	73	F	CYP2C19	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
7	74	M	CYP2D6	*4/*9	Intermediate Metabolizer
			IFNL3	rs12979860T/T	Reduced Response to Hepatitis C Treatment
			CYP2C19	*1/*2	Intermediate Metabolizer
			CYP3A4	*1/*22	Reduced Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
8	59	F	CYP2C9	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			DPYD	*1/rs67376798A	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
9	81	M	CYP3A4	*1/*22	Reduced Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Met/Met	Reduced Stimulant Response
10	79	M	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
11	57	F	CYP2C19	*2/*17	Intermediate to Extensive Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
12	59	M	CYP2C19	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
13	57	F	CYP2C19	*1/*2	Intermediate Metabolizer
			CYP2C9	*1/*3	Intermediate Metabolizer
			F5	F5 Leiden Heterozygous	Increased Thrombophilia Risk
			COMT	Met/Met	Reduced Stimulant Response
14	53	M	CYP2C19	*1/*2	Intermediate Metabolizer
			CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response

(Continues)

TABLE 2 (Continued)

Insight number	Age	Sex	Gene	Genotype	Consequence
15	31	M	CYP2C19	*1/*2	Intermediate Metabolizer
			TPMT	*1/*3A	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
16	61	M	CYP2D6	*1/*2xN	Ultrarapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
17	34	F	CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
18	51	M	CYP2C19	*17/*17	Ultrarapid Metabolizer
			CYP3A4	*1/*22	Reduced Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
19	35	F	CYP2C19	*1/*2	Intermediate Metabolizer
			CYP2C9	*1/*3	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
20	49	M	CYP2C9	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860T/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
21	44	F	CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
22	46	M	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
23	63	M	CYP2D6	*1xN/*35A	Ultrarapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C19	*1/*2	Intermediate Metabolizer
24	74	M	CYP2C19	*1/*17	Rapid Metabolizer
			TPMT	*1/*3A	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
25	71	F	CYP2D6	*2/*2xN	Ultrarapid Metabolizer
			CYP2C19	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860T/T	Reduced Response to Hepatitis C Treatment
			F5	F5 Leiden Heterozygous	Increased Thrombophilia Risk
			COMT	Met/Met	Reduced Stimulant Response
26	59	M	CYP2D6	*9/*5	Intermediate Metabolizer
			CYP2C19	*1/*2	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
27	62	M	CYP2C19	*2/*2	Poor Metabolizer
28	71	F	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860T/T	Reduced Response to Hepatitis C Treatment
			CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response

(Continues)

TABLE 2 (Continued)

Insight number	Age	Sex	Gene	Genotype	Consequence
29	70	F	CYP2C19	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860T/T	Reduced Response to Hepatitis C Treatment
			CYP3A4	*1/*22	Reduced Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
30	69	F	IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
31	61	M	CYP2C19	*1/*2	Intermediate Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
32	55	F	CYP2D6	*4/*5	Poor Metabolizer
			CYP2C9	*1/*2	Intermediate Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
33	67	M	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
34	67	F	CYP2C19	*1/*2	Intermediate Metabolizer
			CYP2C9	*1/*3	Intermediate Metabolizer
			TPMT	*1/*3A	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
35	30	M	CYP2C19	*1/*2	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
36	74	M	CYP2D6	*4/*9	Intermediate Metabolizer
			CYP2C9	*1/*2	Intermediate Metabolizer
			TPMT	*1/*3A	Intermediate Metabolizer
			COMT	Met/Met	Reduced Stimulant Response
37	68	F	CYP2D6	*4/*41	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C19	*1/*17	Rapid Metabolizer
			CYP2C9	*1/*2	Intermediate Metabolizer
			TPMT	*1/*3A	Intermediate Metabolizer
38	63	M	CYP2C19	*2/*17	Intermediate to Extensive Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
39	62	F	CYP2C19	*1/*17	Rapid Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
40	89	F	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
41	34	M	CYP2D6	*4/*5	Poor Metabolizer
			CYP2C19	*1/*2	Intermediate Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
42	88	M	CYP2C19	*1/*17	Rapid Metabolizer
			CYP2C9	*1/*2	Intermediate Metabolizer

(Continues)

TABLE 2 (Continued)

Insight number	Age	Sex	Gene	Genotype	Consequence
43	72	M	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C9	*1/*3	Intermediate Metabolizer
			CYP3A4	*1/*22	Reduced Metabolizer
44	52	M	SEPARATE PHARMACOGENETIC TEST NOT DONE		
45	72	M	CYP2C9	*1/*3	Intermediate Metabolizer
46	56	F	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			COMT	Val/Met	Slightly Reduced Stimulant Response
47	58	F	CYP2C19	*1/*17	Rapid Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			F5	F5 Leiden Heterozygous	Increased Thrombophilia Risk
			COMT	Val/Met	Slightly Reduced Stimulant Response
48	71	M	IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
49	65	F	CYP2C19	*1/*2	Intermediate Metabolizer
			VKORC1	*2/*2	Poor Metabolizer
			CYP3A5	*1/*3	Reduced Metabolizer
50	65	M	CYP2D6	*1/*4	Intermediate Metabolizer
			CYP3A5	*3/*3	Poor Metabolizer
			VKORC1	*3/*4	Increased Metabolizer
			SLCO1B1	*1b/*18	Decreased Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
51	66	F	CYP2C19	*1/*17	Rapid Metabolizer
			CYP3A5	*3/*3	Poor Metabolizer
			VKORC1	*3/*4	Increased Metabolizer
			SLCO1B1	*1a/*15	Decreased Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response
52	77	M	CYP2C19	*2/*17	Intermediate Metabolizer
			IFNL3	rs12979860 C/T	Reduced Response to Hepatitis C Treatment
			CYP2C9	*1/*11	Intermediate Metabolizer
			CYP3A5	*3/*3	Poor Metabolizer
			SLCO1B1	*1a/*18	Decreased Metabolizer
			COMT	Val/Met	Slightly Reduced Stimulant Response

present but was not detected; (2) a heterozygous state may be associated with a phenotype; and (3) these individuals have diseases that are phenocopies of the genetic disorder that they carry. These findings suggest that assessing GS in light of a patient's phenotype may prove useful, arguing that laboratories carrying out elective GS should obtain phenotypic information as we move to comprehensive elective testing(Lu et al., 2019). Individuals who do not have a standard indication for genetic testing may nevertheless have variants resulting in phenotypes related to their medical history.

In 11 cases, 17 VUSs were identified (Table 1). In the case series by Hou et al. (2020), among 42 cases, 44 VUSs were identified. Additional counseling time is required to explain these findings, follow-up testing may incur additional expense, and reassessment of VUSs in the future may be required. VUSs are common in genomic testing (Ziats et al., 2020) and functional assays to assign these variants to the pathogenic or benign category are just beginning to appear (Almeida et al., 2020; Boonen et al., 2019; Drost et al., 2020). As a result, resolution may not be possible currently for many VUSs. Nevertheless, some VUSs can be resolved and are worth pursuing. In case 36, for example, a VUS was found in *SPTLC2 (*605713)*, a gene associated with a treatable disorder (Fridman et al., 2019). Subsequent biochemical

testing concluded that the patient did not have this condition, so the uncertainty about this result was resolved. While many VUSs are likely to be reclassified over time as benign, others will eventually prove to be disease-causing, explaining the patient's phenotype. The opportunity to perform VUS resolution via biochemical testing, imaging, family testing, etc. requires the identification of a VUS in the first place. The identification of VUSs in elective GS relies on thorough phenotyping on the part of the ordering clinician. Importantly, careful phenotyping may identify an aspect of the individual's history or examination where an alternative diagnostic test may be superior to GS.

4.2 | Clonal hematopoiesis of indeterminate potential

Case 38 (age 63) and case 52 (age 77) showed evidence of clonal hematopoiesis of indeterminate potential (CHIP) based on likely pathogenic findings in *TET2 (*612839)* and *ASXL1 (*612990)*, respectively. In both cases, the pathogenic variant allele frequency (VAF) was greater than 10%. CHIP is found in approximately 7–10% of individuals over age 65 and is associated with increased cardiovascular disease due to accelerated atherogenesis and a 0.5% to 1% per year risk of developing a hematologic malignancy (Pinese et al., 2020). Most CHIP-associated pathogenic variants occurred in three epigenetic regulators, *DNMT3A *(602769)*, *TET2*, and *ASXL1*. VAF >10% has a higher risk of cardiovascular disease, indicating that clone size may be correlated with risk (Evans et al., 2020; Fujino & Kitamura, 2020; Karner et al., 2019; Steensma, 2018). In case 38, the patient had a subsequent myocardial event and stent placement.

4.3 | Secondary disease risk

Nine variants that may affect an individual's phenotype in the future were found in eight patients. As seen in Table A1, the percentage of cases harboring an actionable secondary variant varies across studies. This reflects each study's inclusion criteria for this class of variants. In four studies, the authors include pathogenic and in some, likely pathogenic variants expected to be highly penetrant in restricted (Dewey et al., 2016; Natarajan et al., 2016; Van Hout et al., 2020) and unrestricted (Johnston et al., 2016) sets of genes. A more recent study reported secondary variants in 5.8% of cases (Hou et al., 2020). This study included pathogenic and likely pathogenic variants with a wider range of penetrance. Our study included the entire range of variant penetrance as outlined by the ClinGen Low Penetrance/Risk Allele Working Group by including low-, moderate- and high-penetrance variants. All but one of the secondary variants in our cohort would be classified as low or reduced penetrance (ClinGen, xxxx). Case 43 had the only highly penetrant variant, in *BRCA2*. Cases 33 and 48 had the *APC* Ile1307Lys representing an example of a low-penetrance variant. Importantly, certain low-penetrance variants like *APC* Ile1307Lys have established care guidelines (Gupta et al., 2017). Other low- or moderate-penetrance results included variants in *NLRP3 (*606416)*, *WNT10A (*606268)*, *NOD2 (*605956)*, *APOC3 (*107720)*, and *LPL (*609708)*. Until guidelines defining risk cutoffs (odds ratios) for low, moderate, and high penetrance are established, inconsistency in secondary variant reporting will remain.

4.4 | Carrier status

All cases requested carrier status for autosomal recessive or X-linked disorders. Eighty-five percent (44/52) were found to be carriers of disorders that were not related to their phenotype (secondary findings). These 44 individuals were carriers of between 1 and 7 variants (median 2 variants) in 89 genes. We examined a widely available microarray, the Illumina Global Screening Array, a platform that queries variants found in ClinVar. Only 53% of the carrier variants found by GS were represented on the array. As the cost of GS testing falls, couples planning a pregnancy will be able to take advantage of more inclusive screening. Efforts in this direction are underway (Kirk et al., 2019). GS also provides an opportunity for cascade testing of other family members. In our study, many of the participants had children of reproductive age. Laboratories often report both pathogenic and likely pathogenic variants when assessing GS for carrier status. It is unclear whether a likely pathogenic variant should be reported due to the problem of the positive predictive value of such variants in rare disorders (Hagenkord et al., 2020).

4.5 | Pharmacogenetic findings

We obtained pharmacogenetic data from both a stand-alone panel of pharmacogenetic variants and from GS. Some pharmacogenetic variants identified by GS were not included in the pharmacogenetic test; these included variants in *VKORC1 (*608547)*, *DPYD (*612779)*, and *NUDT15 (*615792)*. Case 15 demonstrates the utility of obtaining pharmacogenetic information through GS; in this case, the patient was found to have heterozygous variants in *TPMT (*187680)* and *NUDT15* that in combination would result in significant toxicity if treated with mercaptopurine or thioguanine. In 21 cases, pharmacogenetic testing was relevant to current medication, emphasizing the importance of obtaining patient history in the elective testing setting. At this time, pharmacogenetic testing via GS can be cost-prohibitive due to the need

for Sanger confirmation of variants. With the development of artificial intelligence tools that may make orthogonal confirmation unnecessary, this barrier may be removed in some cases (Holt et al., 2021).

4.6 | Limitations

This study has several limitations. Our small cohort is composed of individuals who are well-educated, generally older, and primarily Caucasian. Nevertheless, their health status was typical for individuals their age and included many common multifactorial diseases. Additionally, a reanalysis of the cases with updated clinical information would likely identify new primary and secondary variants and a reclassification of the pathogenicity of some of the VUSs (Lu et al., 2020). The inclusion of secondary finding variants that are not highly penetrant is also problematic. Assessing whether a variant has moderate penetrance, low penetrance, or should be designated a "risk allele" is not well established, and therefore complicates counseling for these individuals. Understanding how the participants and their physicians used the information from GS was not addressed. These limitations point to the need for longitudinal studies measuring health outcomes, benefits, and cost-effectiveness to assess the value of elective GS.

Establishing the usefulness of elective GS is challenging because of the different measures of utility by different stakeholders. A health insurance company might look for long-term improvement in health outcomes as an essential measure of utility. An individual with a negative result from elective GS may feel reassured that they do not have a well-recognized untreatable genetic disorder and consider this valuable information. A range of utility measures has been proposed reflecting this conundrum (Hayeems et al., 2020). This can be appreciated by examining whether a variant is used in patient care and when it is used. This approach to utility highlights the importance of obtaining the patient's phenotype in elective GS. It should also be noted that not all pathogenic variants are medically important.

As the cost of sequencing falls and as other elective genetic tests become more widespread, we can expect the uptake of elective genetic testing, including GS, to grow dramatically. The clinical utility and personal utility of elective GS will improve with the addition of ancestry assessment, blood groups, human leukocyte antigen typing, and polygenic risk scores. Projects are underway to improve our understanding of variants with various levels of penetrance in the general population (Carlson et al., 2020; Cirulli et al., 2020; Pinese et al., 2020). Reports and online tools geared to the needs of patients and their providers will be required to make the information understandable and provide opportunities to engage with the data as the individuals' medical needs evolve (Yu et al., 2013). With time we can expect to use elective GS across the lifespan (Ceyhan-Birsoy et al., 2019). In addition, if the decreasing cost and increasing quality of sequencing lead to multiple rounds of GS throughout a person's lifetime, the ability to detect somatic variation such as CHIP could add additional value.

5 | CONCLUSION

As the cost of GS falls, its uses in rare disease testing and now elective testing are increasing. A growing body of literature describes the value of elective testing using GS and ES. The case series described here emphasizes the importance of patient phenotype in the analysis of an elective genome, permitting the laboratory to help individuals understand medical conditions already present. The study supports the use of GS to uncover secondary findings including CHIP, disease risk, carrier status, and pharmacogenetics. As demonstrated here, elective genome sequencing allows individuals to realize the promise of personalized medicine.

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CONFLICT OF INTEREST

T.M. is the Chief Scientific Officer and R.M.M. is a co-founder of Kailos Genetics. M.C.S. is consulted for PierianDx. No other authors have conflict(s) of interest to declare.

AUTHORS' CONTRIBUTIONS

R.M. conceived and planned the elective genome sequencing program. M.C., K.E., V.G., W.K., and D.B. evaluated and counseled patients seen in this study. M.K., M.S., and D.B. performed genome analysis. T.M. designed and performed pharmacogenetic analysis. K.O. performed chart review and collected data. M.C. and D.B. designed the study, analyzed and interpreted results, and drafted and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

ETHICAL APPROVAL

Subjects provided written informed consent before participation. The study was approved by the Western Institutional Review Board (WIRB #20161118).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are included in the tables within the manuscript.

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REFERENCES

Almeida, L. G. D., Nanhoe, S., Zonta, A., Hosseinzadeh, M., Kom-Gortat, R., Elfferich, P., Schaaf, G., Kenter, A., Kümmel, D., Migone, N., & Povey, S. (2020). Comparison of the functional and structural characteristics of rare TSC2 variants with clinical and genetic findings. *Human Mutation*, *41*, 759–773.

Ball, M. P., Thakuria, J. V., Zaranek, A. W., Clegg, T., Rosenbaum, A. M., Wu, X., Angrist, M., Bhak, J., Bobe, J., Callow, M. J., Cano, C., Chou, M. F., Chung, W. K., Douglas, S. M., Estep, P. W., Gore, A., Hulick, P., Labarga, A., Lee, J.-H., … Church, G. M. (2012). A public resource facilitating clinical use of genomes. *Proceedings of the National Academy of Sciences of the United States of America.*, *109*, 11920–11927. https://doi.org/10.1073/pnas.1201904109

Baptista, N. M., Christensen, K. D., Carere, D. A., Broadley, S. A., Roberts, J. S., & Green, R. C. (2016). Adopting genetics: motivations and outcomes of personal genomic testing in adult adoptees. *Genetics in Medicine*, *18*, 924–932. https://doi.org/10.1038/gim.2015.192

Bick, D., Jones, M., Taylor, S. L., Taft, R. J., & Belmont, J. (2019). Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. *Journal of Medical Genetics*, *56*, 783–791. https://doi.org/10.1136/jmedgenet-2019-106111

Boonen, R. A. C. M., Rodrigue, A., Stoepker, C., Wiegant, W. W., Vroling, B., Sharma, M., Rother, M. B., Celosse, N., Vreeswijk, M. P. G., Couch, F., Simard, J., Devilee, P., Masson, J.-Y., & van Attikum, H. (2019). Functional analysis of genetic variants in the high-risk breast cancer susceptibility gene PALB2. *Nature Communications*, *10*(1). https://doi.org/10.1038/s41467-019-13194-2

Carlson, P., Wojczynski, M. K., Druley, T., Lee, J. H., Zmuda, J. M., & Thyagarajan, B. (2020). Prevalence of clinically actionable disease variants in exceptionally long-lived families. *BMC Medical Genomics*, *13*, 61. https://doi.org/10.1186/s12920-020-0710-5

Ceyhan-Birsoy, O., Murry, J. B., Machini, K., Lebo, M. S., Yu, T. W., Fayer, S., Genetti, C. A., Schwartz, T. S., Agrawal, P. B., Parad, R. B., Holm, I. A., McGuire, A. L., Green, R. C., Rehm, H. L., Beggs, A. H., Agrawal, P. B., Beggs, A. H., Betting, W. N., Ceyhan-Birsoy, O., … Yu, T. W. (2019). Interpretation of genomic sequencing results in healthy and Ill newborns: Results from the BabySeq Project. *American Journal of Human Genetics*, *104*, 76–93. https://doi.org/10.1016/j.ajhg.2018.11.016

Chen, R., Mias, G. I., Li-Pook-Than, J., Jiang, L., Lam, H. Y. K., Chen, R., Miriami, E., Karczewski, K. J., Hariharan, M., Dewey, F. E., Cheng, Y., Clark, M. J., Im, H., Habegger, L., Balasubramanian, S., O'Huallachain, M., Dudley, J. T., Hillenmeyer, S., Haraksingh, R., … Snyder, M. (2012). Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell*, *148*, 1293–1307. https://doi.org/10.1016/j.cell.2012.02.009

Chen, X., Zhang, Y., Wang, F., Wang, M., Teng, W., Lin, Y., Han, X., Jin, F., Xu, Y., Cao, P., Fang, J., Zhu, P., Tong, C., & Liu, H. (2017). Germline cytotoxic lymphocytes defective mutations in Chinese patients with lymphoma. *Oncology Letters*, *14*, 5249–4246. https://doi.org/10.3892/ol.2017.6898

Ciambotti, B., Mussolin, L., d'Amore, E. S. G., Pillon, M., Sieni, E., Coniglio, M. L., Ros, M. D., Cetica, V., Aricò, M., & Rosolen, A. (2014). Monoallelic mutations of the perforin gene may represent a predisposing factor to childhood anaplastic large cell lymphoma. *Journal of Pediatric Hematology/oncology*, *36*, e359–e365. https://doi.org/10.1097/MPH.0000000000000073

Cirulli, E. T., White, S., Read, R. W., Elhanan, G., Metcalf, W. J., Tanudjaja, F., Fath, D. M., Sandoval, E., Isaksson, M., Schlauch, K. A., Grzymski, J. J., Lu, J. T., & Washington, N. L. (2020). Genome-wide rare variant analysis for thousands of phenotypes in over 70,000 exomes from two cohorts. *Nature Communications*, *11*, 542. https://doi.org/10.1038/s41467-020-14288-y

Clementi, R., Dagna, L., Dianzani, U., Dupré, L., Dianzani, I., Ponzoni, M., Cometa, A., Chiocchetti, A., Sabbadini, M. G., Rugarli, C., Ciceri, F., Maccario, R., Locatelli, F., Danesino, C., Ferrarini, M., & Bregni, M. (2004). Inherited perforin and Fas mutations in a patient with autoimmune lymphoproliferative syndrome and lymphoma. *New England Journal of Medicine*, *351*(14), 1419–1424. https://doi.org/10.1056/nejmoa041432.

ClinGen. Low Penetrance/Risk Allele Working Group. https://clinicalgenome.org/site/assets/files/4531/clingenrisk_terminology_recomendations-final-02_18_20.pdf

Cremers, F. P. M., Lee, W., Collin, R. W. J., & Allikmets, R. (2020). Clinical spectrum, genetic complexity and therapeutic approaches for retinal disease caused by ABCA4 mutations. *Progress in Retinal and Eye Research*, *79*, 100861. https://doi.org/10.1016/j.preteyeres.2020.100861

Dewey, F. E., Grove, M. E., Pan, C., Goldstein, B. A., Bernstein, J. A., Chaib, H., Merker, J. D., Goldfeder, R. L., Enns, G. M., David, S. P., Pakdaman, N., Ormond, K. E., Caleshu, C., Kingham, K., Klein, T. E., Whirl-Carrillo, M., Sakamoto, K., Wheeler, M. T., Butte, A. J., … Quertermous, T. (2014). Clinical interpretation and implications of whole-genome sequencing. *JAMA*, *311*, 1035–1045. https://doi.org/10.1001/jama.2014.1717

Dewey, F. E., Murray, M. F., Overton, J. D., Habegger, L., Leader, J. B., Fetterolf, S. N., O'Dushlaine, C., Van Hout, C. V., Staples, J., Gonzaga-Jauregui, C., Metpally, R., Pendergrass, S. A., Giovanni, M. A., Kirchner, H. L., Balasubramanian, S., Abul-Husn, N. S., Hartzel, D. N., Lavage, D. R., Kost, K. A., … Carey, D. J. (2016). Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. *Science*, *354*(6319), aaf6814. https://doi.org/10.1126/science.aaf6814

Ding, Q., & Yang, L.-Y. (2013). Perforin gene mutations in 77 Chinese patients with lymphomas. *World Journal of Emergency Medicine*, *4*, 128–132. https://doi.org/10.5847/wjem.j.issn.1920-8642.2013.02.008

Drost, M., Tiersma, Y., Glubb, D., Kathe, S., van Hees, S., Calléja, F., Zonneveld, J. B. M., Boucher, K. M., Ramlal, R. P. E., Thompson, B. A., Rasmussen, L. J., Greenblatt, M. S., Lee, A., Spurdle, A. B., Tavtigian, S. V., & de Wind, N. (2020). Two integrated and highly predictive functional analysis-based procedures for the classification of MSH6 variants in Lynch syndrome. *Genetics in Medicine*, *22*, 847–856. https://doi.org/10.1038/s41436-019-0736-2

East, K. M., Cochran, M., Kelley, W. V., Greve, V., Emmerson, K., Raines, G., Cochran, J. N., Hott, A. M., & Bick, D. (2019). Understanding the present and preparing for the future: Exploring the needs of diagnostic and elective genomic medicine patients. *Journal of Genetic Counseling*, *28*, 438–448. https://doi.org/10.1002/jgc4.1114

Evans, M. A., Sano, S., & Walsh, K. (2020). Cardiovascular disease, aging, and clonal hematopoiesis. *Annual Review of Pathology: Mechanisms of Disease*, *15*, 419–438. https://doi.org/10.1146/annurev-pathmechdis-012419-032544

Fiala, C., Taher, J., & Diamandis, E. P. (2019). P4 medicine or O4 medicine? Hippocrates provides the answer. *The Journal of Applied Laboratory Medicine*, *4*, 108–119. https://doi.org/10.1373/jalm.2018.028613

Flemin, J., Terrill, B., Dziadek, M., Kirk, E. P., Roscioli, T., & Barlow-Stewart, K. (2019). Personal genomic screening: How best to facilitate preparedness of future clients. *European Journal of Medical Genetics*, *62*(5), 397–404. https://doi.org/10.1016/j.ejmg.2019.05.006

Fridman, V., Suriyanarayanan, S., Novak, P., David, W., Macklin, E. A., McKenna-Yasek, D., Walsh, K., Aziz-Bose, R., Oaklander, A. L., Brown, R., Hornemann, T., & Eichler, F. (2019). Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. *Neurology*, *92*(4), e359–e370. https://doi.org/10.1212/wnl.0000000000006811

Fujino, T., & Kitamura, T. (2020). $ASXL_1$ mutation in clonal hematopoiesis. *Experimental Hematology*, *83*, 74–84. https://doi.org/10.1016/j.exphem.2020.01.002

Gonzalez-Garay, M. L., McGuire, A. L., Pereira, S., & Caskey, C. T. (2013). Personalized genomic disease risk of volunteers. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 16957–16962. https://doi.org/10.1073/pnas.1315934110

Gupta, S., Provenzale, D., Regenbogen, S. E., Hampel, H., Slavin, T. P., Hall, M. J., Llor, X., Chung, D. C., Ahnen, D. J., Bray, T., Cooper, G., Early, D. S., Ford, J. M., Giardiello, F. M., Grady, W., Halverson, A. L., Hamilton, S. R., Klapman, J. B., Larson, D. W., … Ogba, N. (2017). NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017. *Journal of the National Comprehensive Cancer Network*, *15*(12), 1465–1475. https://doi.org/10.6004/jnccn.2017.0176

Hagenkord, J., Funke, B., Qian, E., Hegde, M., Jacobs, K. B., Ferber, M., Lebo, M., Buchanan, A., & Bick, D. (2020). Design and reporting considerations for genetic screening tests. *The Journal of Molecular Diagnostics*, *22*, 599–609. https://doi.org/10.1016/j.jmoldx.2020.01.014

Hayeems, R. Z., Dimmock, D., Bick, D., Belmont, J. W., Green, R. C., Lanpher, B., Jobanputra, V., Mendoza, R., Kulkarni, S., Grove, M. E., Taylor, S. L., & Ashley, E. (2020). Clinical utility of genomic sequencing: a measurement toolkit. *NPJ Genomic Medicine*, *5*(1), 1–11. https://doi.org/10.1038/s41525-020-00164-7

Holt, J. M., Kelly, M., Sundlof, B., Nakouzi, G., Bick, D., & Lyon, E. (2021). Reducing Sanger Confirmation Testing through False Positive Prediction Algorithms. *Genetics in Medicine*, *23*(7), 1255–1262. https://doi.org/10.1038/s41436-021-01148-3

Hou, Y.-C.-C., Yu, H.-C., Martin, R., Cirulli, E. T., Schenker-Ahmed, N. M., Hicks, M., Cohen, I. V., Jönsson, T. J., Heister, R., Napier, L., Swisher, C. L., Dominguez, S., Tang, H., Li, W., Perkins, B. A., Barea, J., Rybak, C., Smith, E., Duchicela, K., … Caskey, C. T. (2020). Precision medicine integrating whole-genome sequencing, comprehensive metabolomics, and advanced imaging. *Proceedings of the National Academy of Sciences of the United States of America*, *117*, 3053–3062. https://doi.org/10.1073/pnas.1909378117

https://en.wikipedia.org/wiki/Elective_genetic_and_genomic_testing

https://gatk.broadinstitute.org/hc/en-us

https://hudsonalpha.org/codicem

Jarmula, A., Łusakowska, A., Fichna, J. P., Topolewska, M., Macias, A., Johnson, K., Töpf, A., Straub, V., Rosiak, E., Szczepaniak, K., Dunin-Horkawicz, S., Maruszak, A., Kaminska, A. M., & Redowicz, M. J. (2019). ANO5 mutations in the Polish limb girdle muscular dystrophy patients: Effects on the protein structure. *Scientific Reports*, *9*, 11533. https://doi.org/10.1038/s41598-019-47849-3

Jochim, A., Zech, M., Gora-Stahlberg, G., Winkelmann, J., & Haslinger, B. (2016). The clinical phenotype of early-onset isolated dystonia caused by recessiveCOL6A3mutations (DYT27). *Movement Disorders*, *31*(5), 747–750. https://doi.org/10.1002/mds.26501

Johnston, J. J., Lewis, K. L., Ng, D., Singh, L. N., Wynter, J., Brewer, C., Brooks, B. P., Brownell, I., Candotti, F., Gonsalves, S. G., Hart, S. P., Kong, H. H., Rother, K. I., Sokolic, R., Solomon, B. D., Zein, W. M., Cooper, D. N., Stenson, P. D., Mullikin, J. C., & Biesecker, L. G. (2015). Individualized iterative phenotyping for genome-wide analysis of loss-of-function mutations. *American Journal of Human Genetics*, *96*, 913–925. https://doi.org/10.1016/j.ajhg.2015.04.013

Johnston, J. J., Lewis, K. L., Ng, D., Singh, L. N., Wynter, J., Brewer, C., Brooks, B. P., Brownell, I., Candotti, F., Gonsalves, S. G., Hart, S. P., Kong, H. H., Rother, K. I., Sokolic, R., Solomon, B. D., Zein, W. M., Cooper, D. N., Stenson, P. D., Mullikin, J. C., & Biesecker, L. G. (2016). Individualized iterative phenotyping for genome-wide analysis of loss-of-function mutations. *American Journal of Human Genetics*, *96*, 913–925. https://doi.org/10.1016/j.ajhg.2015.04.013

Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., Herman, G. E., Hufnagel, S. B., Klein, T. E., Korf, B. R., McKelvey, K. D., Ormond, K. E., Richards, C. S., Vlangos, C. N., Watson, M., Martin, C. L., & Miller, D. T. (2017). 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. *Genetics in Medicine*, *19*(2), 249–255. https://doi.org/10.1038/gim.2016.190

Karner, K., George, T. I., & Patel, J. L. (2019). Current aspects of clonal hematopoiesis: Implications for clinical diagnosis. *Annals of Laboratory Medicine*, *39*, 509–514. https://doi.org/10.3343/alm.2019.39.6.509

Kirk, E. P., Barlow-Stewart, K., Selvanathan, A., Josephi-Taylor, S., Worgan, L., Rajagopalan, S., Cowley, M. J., Gayevskiy, V., Bittles, A., Burnett, L., Elakis, G., Lo, W., Buckley, M., Colley, A., & Roscioli, T. (2019). Beyond the panel: preconception screening in consanguineous couples using the TruSight One "clinical exome". *Genetics in Medicine*, *21*, 608–612. https://doi.org/10.1038/s41436-018-0082-9

Lewis, K. L., Hooker, G. W., Connors, P. D., Hyams, T. C., Wright, M. F., Caldwell, S., Biesecker, L. G., & Biesecker, B. B. (2016). Participant use and communication of findings from exome sequencing: a mixed-methods study. *Genetics in Medicine*, *18*, 577–583. https://doi.org/10.1038/gim.2015.133

Lu, C. Y., Hendricks-Sturrup, R. M., Mazor, K. M., McGuire, A. L., Green, R. C., & Rehm, H. L. (2020). The case for implementing sustainable routine, population-level genomic reanalysis. *Genetics in Medicine*, *22*(4), 815–816. https://doi.org/10.1038/s41436-019-0719-3

Lu, J. T., Ferber, M., Hagenkord, J., Levin, E., South, S., Kang, H. P., Strong, K. A., & Bick, D. P. (2019). Evaluation for Genetic Disorders in the Absence of a Clinical Indication for Testing: Elective Genomic Testing. *The Journal of Molecular Diagnostics*, *21*, 3–12. https://doi.org/10.1016/j.jmoldx.2018.09.006

Lupo, P. J., Robinson, J. O., Diamond, P. M., Jamal, L., Danysh, H. E., Blumenthal-Barby, J., Lehmann, L. S., Vassy, J. L., Christensen, K. D., Green, R. C., & McGuire, A. L. (2016). Patients' perceived utility of whole-genome sequencing for their healthcare: findings from the MedSeq project. *Per Med.*, *13*, 13–20. https://doi.org/10.2217/pme.15.45

Machini, K., Ceyhan-Birsoy, O., Azzariti, D. R., Sharma, H., Rossetti, P., Mahanta, L., Hutchinson, L., McLaughlin, H., Green, R. C., Lebo, M., & Rehm, H. L. (2019). Analyzing and reanalyzing the genome: Findings from the MedSeq Project. *American Journal of Human Genetics*, *105*, 177–188. https://doi.org/10.1016/j.ajhg.2019.05.017

Natarajan, P., Gold, N. B., Bick, A. G., McLaughlin, H., Kraft, P., Rehm, H. L., Peloso, G. M., Wilson, J. G., Correa, A., Seidman, J. G., Seidman, C. E., Kathiresan, S., & Green, R. C. (2016). Aggregate penetrance of genomic variants for actionable disorders in European and African Americans. *Science Translational Medicine*, *8*(364), 364ra151. https://doi.org/10.1126/scitranslmed.aag2367

Panda, P. K., & Sharawat, I. K. (2020). $COL6A_3$ mutation associated early-onset isolated dystonia (DYT)-27: Report of a new case and review of published literature. *Brain and Development*, *42*, 329–335. https://doi.org/10.1016/j.braindev.2020.01.004

Penttilä, S., Vihola, A., Palmino, J., & Udd, B. (2012). ANO5 Muscle Disease. *GeneReviews* (Internet).

Pinese, M., Lacaze, P., Rath, E. M., Stone, A., Brion, M.-J., Ameur, A., Nagpal, S., Puttick, C., Husson, S., Degrave, D., Cristina, T. N., Kahl, V. F. S., Statham, A. L., Woods, R. L., McNeil, J. J., Riaz, M., Barr, M., Nelson, M. R., Reid, C. M., … Thomas, D. M. (2020). The Medical Genome Reference Bank contains whole genome and phenotype data of 2570 healthy elderly. *Nature Communications*, *11*, 435. https://doi.org/10.1038/s41467-019-14079-0

Price, N. D., Magis, A. T., Earls, J. C., Glusman, G., Levy, R., Lausted, C., McDonald, D. T., Kusebauch, U., Moss, C. L., Zhou, Y., Qin, S., Moritz, R. L., Brogaard, K., Omenn, G. S., Lovejoy, J. C., & Hood, L. (2017). A wellness study of 108 individuals using personal, dense, dynamic data clouds. *Nature Biotechnology*, *8*, 747–756. https://doi.org/10.1038/nbt.3870

Rego, S., Dagan-Rosenfeld, O., Zhou, W., Sailani, M. R., Limcaoco, P., Colbert, E., Avina, M., Wheeler, J., Craig, C., Salins, D., Röst, H. L., Dunn, J., McLaughlin, T., Steinmetz, L. M., Bernstein, J. A., & Snyder, M. P. (2018). High-frequency actionable pathogenic exome variants in an average-risk cohort. *Cold Spring Harbor Molecular Case Studies*, *4*, a003178. https://doi.org/10.1101/mcs.a003178

Reuter, M. S., Walker, S., Thiruvahindrapuram, B., Whitney, J., Cohn, I., Sondheimer, N., Yuen, R. K. C., Trost, B., Paton, T. A., Pereira, S. L., Herbrick, J.-A., Wintle, R. F., Merico, D., Howe, J., MacDonald, J. R., Lu, C., Nalpathamkalam, T., Sung, W. W. L., Wang, Z., … Scherer, S. W. (2018). The Personal Genome Project Canada: Findings from whole genome sequences of the inaugural 56 participants. *Canadian Medical Association Journal*, *190*, E126–E136. https://doi.org/10.1503/cmaj.171151

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2016). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*, 405–424. https://doi.org/10.1038/gim.2015.30

Roberts, J. S., Robinson, J. O., Diamond, P. M., Bharadwaj, A., Christensen, K. D., Lee, K. B., Green, R. C., & McGuire, A. L. (2018). Patient understanding of, satisfaction with, and perceived utility of whole-genome sequencing: findings from the MedSeq Project. *Genetics in Medicine*, *20*, 1069–1076. https://doi.org/10.1038/gim.2017.223

Sanderson, S. C., Linderman, M. D., Suckiel, S. A., Diaz, G. A., Zinberg, R. E., Ferryman, K., Wasserstein, M., Kasarskis, A., & Schadt, E. E. (2016). Motivations, concerns and preferences of personal genome sequencing research participants: Baseline findings from the HealthSeq project. *European Journal of Human Genetics*, *24*, 14–20. https://doi.org/10.1038/ejhg.2015.118

Savarese, M., Di Fruscio, G., Tasca, G., Ruggiero, L., Janssens, S., De Bleecker, J., Delpech, M., Musumeci, O., Toscano, A., Angelini, C., Sacconi, S., Santoro, L., Ricci, E., Claes, K., Politano, L., & Nigro, V. (2016). Next generation sequencing on patients with LGMD and nonspecific myopathies: Findings associated with ANO5 mutations. *Neuromuscular Disorders*, *25*, 533–541. https://doi.org/10.1016/j.nmd.2015.03.011

Steensma, D. P. (2018). Clinical consequences of clonal hematopoiesis of indeterminate potential. *Blood Advances*, *2*, 3404–3410. https://doi.org/10.1182/bloodadvances.2018020222

Tesi, B., Chiang, S. C. C., El-Ghoneimy, D., Hussein, A. A., Langenskiöld, C., Wali, R., Fadoo, Z., Silva, J. P., Lecumberri, R., Unal, S., Nordenskjöld, M., Bryceson, Y. T., Henter, J., & Meeths, M. (2015). Spectrum of A typical Clinical Presentations in Patients with Biallelic PRF1 Missense Mutations. *Pediatric Blood & Cancer*, *62*(12), 2094–2100. http://dx.doi.org/10.1002/pbc.25646.

Van Hout, C. V., Tachmazidou, I., Backman, J. D., Hoffman, J. D., Liu, D., Pandey, A. K., Gonzaga-Jauregui, C., Khalid, S., Ye, B., Banerjee, N., Li, A. H., O'Dushlaine, C., Marcketta, A., Staples, J., Schurmann, C., Hawes, A., Maxwell, E., Barnard, L., Lopez, A., … Baras, A. (2020). Exome sequencing and characterization of 49,960 individuals in the UK Biobank. *Nature*, *586*(7831), 749–756. https://doi.org/10.1038/s41586-020-2853-0

van Rooij, J., Arp, P., Broer, L., Verlouw, J., van Rooij, F., Kraaij, R., Uitterlinden, A., & Verkerk, A. J. (2020). Reduced penetrance of athogeneic ACMG variants in a deeply phenotyped cohort study and evaluation of ClinVar Classification over time. *Genetics in Medicine*, *22*(11), 1812–1820.

Worthey, E. A. (2017). Analysis and annotation of whole-genome or whole-exome sequencing derived variants for clinical diagnosis. *Current Protocols in Human Genetics*, *95*, 9.24.1–9.24.28.

Yu, J.-H., Jamal, S. M., Tabor, H. K., & Bamshad, M. J. (2013). Self-guided management of exome and whole-genome sequencing results: changing the results return model. *Genetics in Medicine*, *15*, 684–690. https://doi.org/10.1038/gim.2013.35

Zech, M., Lam, D. D., Francescatto, L., Schormair, B., Salminen, A. V., Jochim, A., Wieland, T., Lichtner, P., Peters, A., Gieger, C., Lochmüller, H., Strom, T. M., Haslinger, B., Katsanis, N., & Winkelmann, J. (2015). Recessive mutations in the α3 (VI) collagen gene $COL6A_3$ cause early-onset isolated dystonia. *American Journal of Human Genetics*, *96*, 883–893. https://doi.org/10.1016/j.ajhg.2015.04.010

Zernant, J., Lee, W., Collison, F. T., Fishman, G. A., Sergeev, Y. V., Schuerch, K., Sparrow, J. R., Tsang, S. H., & Allikmets, R. (2017). Frequent hypomorphic alleles account for a significant fraction of $ABCA_4$ disease and distinguish it from age-related macular degeneration. *Journal of Medical Genetics*, *54*, 404–412. https://doi.org/10.1136/jmedgenet-2017-104540

Ziats, M. N., Ahmad, A., Bernat, J. A., Fisher, R., Glassford, M., Hannibal, M. C., Jacher, J. E., Weiser, N., Keegan, C. E., Lee, K. N., Marzulla, T. B., O'Connor, B. C., Quinonez, S. C., Seemann, L., Turner, L., Bielas, S., Harris, N. L., Ogle, J. D., Innis, J. W., & Martin, D. M. (2020). Genotype-phenotype analysis of 523 patients by genetics evaluation and clinical exome sequencing.

Pediatric Research, *76*, 735–739. https://doi.org/10.1038/s41390-019-0611-5

Zoltick, E. S., Linderman, M. D., McGinniss, M. A., Ramos, E., Ball, M. P., Church, G. M., Leonard, D. G. B., Pereira, S., McGuire, A. L., Caskey, C. T., Sanderson, S. C., Schadt, E. E., Nielsen, D. E., Crawford, S. D., & Green, R. C. (2019). Predispositional genome sequencing in healthy adults: design, participant characteristics, and early outcomes of the PeopleSeq Consortium. *Genome Medicine*, *11*, 10. https://doi.org/10.1186/s13073-019-0619-9

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APPENDIX A

TABLE A1 Elective genome and elective exome studies.

Study	Publication date	# of Subjects enrolled in the study	GS versus ES	Medical history	Family history
Chen et al. (2012)	2012	1	GS	Yes	No
Ball et al. (2012)	2012	10	GS	Yes	Yes
Gonzalez-Garay et al. (2013)	2013	81	ES	Yes	Yes
Dewey et al. (2014)	2014	12	GS	Yes	Yes
Johnston et al. (2015)	2015	951	ES	Yes	Yes
Reuter et al. (2018)	2018	56	GS	Yes	Yes
Rego et al. (2018)	2018	70	ES	Yes	Yes
Machini et al. (2019)	2019	100	GS	Yes	Yes
Hou et al. (2020)	2020	1,190	GS	Yes	Yes
Pinese et al. (2020)	2020	2,570	GS	Yes	No
van Rooij et al. (2020)	2020	2628	ES	Yes	No

Medical History: A medical history was obtained from each individual enrolled in the study. Family History: A family history was obtained for each individual enrolled in the study.

Abbreviation: GS, genome sequencing; ES, exome sequencing.