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** | **ICD10** | **Variant category** | **Gene** |
| **number** | **Age** | **Sex** | **Description** | | |
| 1 | 55 | F | Oth Disorders Of Plasma-Protein Metabolism, Nec E88.09 | Pharmacogenetic | BCHE |
|  |  |  | Sleep Apnea, Unspecified G47.30 | Secondary Carrier | CNGB3 |
|  |  |  | Restless Legs Syndrome G25.81 |  |  |
|  |  |  | Dysthymic Disorder F34.1 |  |  |
| 2 | 69 | F | Giant Cell Arteritis With Polymyalgia Rheumatica M31.5 | Secondary Carrier | BBS1 |
|  |  |  |  | Secondary Carrier | RNASEH2B |
|  |  |  |  | Secondary Carrier | 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 | Secondary Carrier | GCDH |
|  |  |  | Dysthymic Disorder F34.1 | Secondary Carrier | CLCN1 |
|  |  |  |  | Secondary Carrier | ASB10 |
| 6 | 73 | F | Parkinson's Disease G20 | no reportable variants identified |  |
|  |  |  | Abnormal Weight Loss R63.4 |  |  |
|  |  |  | Unspecified Age-Related Cataract H25.9 |  |  |
|  |  |  | Unspecified Sensorineural Hearing Loss H90.5 |  |  |
|  |  |  | Unspecified Dementia Without Behavioral Disturbance F03.90 |  |  |
| 7 | 74 | M | Malignant Neoplasm Of Prostate C61 | Primary | MSR1 |
|  |  |  | Low Back Pain M54.5 | Secondary Carrier | SERPIN A1 |
|  |  |  | Unspecified Atrial Fibrillation I48.91 |  |  |
|  |  |  | Dyrtcol 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 |  |  |
| 8 | 59 | F | Exercise Induced Bronchospasm J45.990 | Secondary Carrier | GPSM2 |
|  |  |  | Celiac Disease K90.0 |  |  |
| 9 | 81 | M | Malignant Neoplasm Of Prostate C61 | Primary | MSR1 |
|  |  |  | Unspecified Sensorineural Hearing Loss H90.5 | Secondary Carrier | SLC45A 2 |
|  |  |  | Unspecified Cataract H26.9 | Secondary Carrier | GALC |
|  |  |  | Frequency Of Micturition R35.0 |  |  |
| 10 | 79 | M | Age-Related Cognitive Decline R41.81 | no reportable variants identified |  |
|  |  |  | Unspecified Age-Related Cataract H25.9 |  |  |
|  |  |  | Low Back Pain M54.5 |  |  |
|  |  |  | Pain In Unspecified Hip M25.559 |  |  |
|  |  |  | Other Chronic Sinusitis J32.8 |  |  |
| 11 | 57 | F | Syncope And Collapse R55 | Primary | NKX2-5 |
|  |  |  | Renal Agenesis, Unilateral Q60.0 | Secondary Carrier | NM_001166176 |
|  |  |  | Congenital Absence Of Ovary, Unilateral Q50.01 |  |  |
| 12 | 59 | M | Old Myocardial Infarction I25.2 | Secondary Carrier | HFE |
|  |  |  | Tinea Unguim B35.1 | Secondary Carrier | GAA |
|  |  |  | 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 |  |  |
| 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 | T383His*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_000142768 | 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)
| Participant information | Variant information |
|-------------------------|---------------------|
| **Insight number** | **Age** | **Sex** | **ICD10** | **Variant category** | **Gene** |
| 13 | 57 | F | Other Types Of Non-Hodg Lymph, Nodes Of Head, Face, And Neck C85.81 | Primary | F5 |
| | | | Hyperlipidemia, Unspecified E78.5 | Primary | PRF1 |
| | | | Hyperthyroidism, Unspecified E03.9 | Secondary Carrier | SERPIN A1 |
| | | | Acute Embolism And Thrombosis Of Other Thoracic Veins I82.290 | Secondary Carrier | MVK |
| | | | | Secondary Carrier | TMPRSS3 |
| 14 | 53 | M | Chronic Ischemic Heart Disease, Unspecified I25.9 | Primary | WNT10A |
| | | | Essential (primary) Hypertension I10 | Secondary Carrier | PYGM |
| | | | Hyperlipidemia, Unspecified E78.5 | Secondary Carrier | TYR |
| | | | Gastro-Esophageal Reflux Disease Without Esophagitis K21.9 | Secondary Carrier | ATM |
| | | | | | |
| 15 | 31 | M | Acne Vulgaris L70.0 | Pharmacogenetic | TPMT |
| | | | Mild Intermittent Asthma, Uncomplicated J45.20 | Pharmacogenetic | TPMT |
| | | | Tension-Type Headache, Unspecified, Not Intractable G44.20 | Pharmacogenetic | NUDT15 |
| 16 | 61 | M | Gastro-Esophageal Reflux Disease Without Esophagitis K21.9 | Secondary Carrier | ACADM |
| | | | Essential (primary) Hypertension I10 | Secondary Carrier | C5orf42 |
| | | | Obstructive Sleep Apnea (adult) (pediatric) G47.33 | Secondary Carrier | COL4A3 |
| | | | | Secondary Carrier | JAGN1 |
| | | | | Secondary Carrier | ATM |
| 17 | 34 | F | Anxiety Disorder, Unspecified F41.9 | no reportable variants identified | |
| | | | Hypothyroidism, Unspecified E03.9 | | |
| | | | Attention-Deficit Hyperactivity Disorder, Unspecified Type F90.9 | | |
| 18 | 51 | M | Pure Hypercholesterolemia, Unspecified E78.00 | Secondary Carrier | MTFMT |
| | | | Essential (primary) Hypertension I10 | Secondary Carrier | SERPINA1 |
| | | | Disorder Of Bilirubin Metabolism, Unspecified E80.7 | | |
| | | | Allergy To Peanuts Z91.010 | | |
| 19 | 35 | F | Calculus Of Kidney N20.0 | Primary | CYP24A1 |
| | | | | Secondary Carrier | HFE |
| | | | | Secondary Carrier | RNASEH2B |
| | | | | Secondary Carrier | SLC26A3 |
| | | | | Secondary Carrier | WDR72 |
| 20 | 49 | M | Essential (primary) Hypertension I10 | Secondary Carrier | FGB |
| | | | | Secondary Carrier | IDUA |
| | | | | Secondary Carrier | TG |
| 21 | 44 | F | Eclampsia Complicating The Puerperium O15.2 | Secondary Carrier | AGXT |
| | | | Malignant Neoplasm Of Unsp Site Of Unspecified Female Breast C50.919 | Secondary Carrier | CBS |
| | | | Supraventricular Tachycardia I47.1 | Secondary Carrier | DHCR7 |
| | | | | Secondary Carrier | 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 | Secondary Carrier | CYP17A1 |
| | | | Noise Effects On Left Inner Ear H83.3X2 | Secondary Disease | 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_000051       | chr11:g.108121753_108121754delAG | 1561_1562delAG   | E522I              | 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.491C>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_107412535insTGA  | c.2026_2027dupTCA| p.Ile675dup       | Likely Pathogenic      |
| NM_018081.2     | chr17:g.7591983_7591984delICT     | c.17_18delICT    | p.Gln7ThrfsTer27  | Likely Pathogenic      |
| NM_005141.4     | chr4:g.155486984C>T               | c.139C>T         | p.Arg477Ter       | 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.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_104596942insT   | c.177dupA        | p.Tyr60IlefsTer29 | Likely Pathogenic      |
| NM_025216.2     | chr2:g.219755011T>A               | c.682T>A         | p.Phe228Ile       | Pathogenic             |
| Participant information | Variant information |
|-------------------------|---------------------|
| Insight number | Age | Sex | ICD10 | Variant category | Gene |
| 24 | 74 | M | Rheumatoid arthritis M05.89 | Primary | CLEC7A |
| & Onychomycosis B35.1 | Secondary Carrier | GAA |
| & Gallstones K80.0 | Secondary Carrier | USH2A |
| & Kidney stones N20.0 | Pharmacogenetic | TMPT*3A |
| | Pharmacogenetic | TMPT*3A |
| | Pharmacogenetic | CYP2D6*6 |
| | Pharmacogenetic | CYP2C19*17 |
| | Pharmacogenetic | UGT1A1*80 |
| 25 | 71 | F | Major Depressive Disorder F33.9 | Secondary Carrier | MED25 |
| & Interstitial Pulmonary Disease J84.9 | |
| 26 | 59 | M | Paroxysmal Atrial Fibrillation I48.0 | Secondary Disease | WNT10A |
| & Essential Hypertension I10 | |
| & Benign Neoplasm of Cerebral Meninges D32.0 | |
| 27 | 62 | M | Benign prostatic hypertrophy N40.1 | Secondary Disease | APOC3 |
| & Age-related cognitive decline R41.84 | Secondary Carrier | GJB2 |
| | Secondary Carrier | LOXHD1 |
| | Pharmacogenetic | CYP2C19 |
| | Pharmacogenetic | SLC01B1 |
| | Pharmacogenetic | VKORC1 |
| 28 | 71 | F | Other Specified Forms of Tremor G25.2 | Secondary Carrier | TYR |
| & 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 | |
| 29 | 70 | F | Malignant Neoplasm of Breast C50.919 | Primary | PER3 |
| & Family History of Epilepsy and Other Disease of the Nervous System Z82.0 | Primary | PER3 |
| | Secondary Carrier | SERPINA1 |
| | Secondary Carrier | SLC7A9 |
| 30 | 69 | F | Primary Osteoarthritis, Right Hand M19.041 | Secondary Carrier | RSPH1 |
| & Primary Osteoarthritis, Left Hand 19.042 | Secondary Carrier | TACR3 |
| & Pure Hypercholesterolemia E78.00 | |
| & Sensorineural HL, Unilateral H90.42 | |
| & Cyclic Vomiting, Not Intractable G43.A0 | |
| 31 | 61 | M | Pure Hypercholesterolemia, Unspecified E78.00 | Secondary Carrier | ACADM |
| & Essential (primary) Hypertension I10 | Secondary Carrier | EVC2 |
| | Secondary Disease | SLC3A1 |
| | Secondary Carrier | USH2A |
| | Secondary Carrier | ALG12 |
| | Secondary Carrier | 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.216497852C>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  | chr2:219755011T>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_00372.4   | 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)
| Participant Information | Variant Information |
|-------------------------|---------------------|
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 32 | 55 | F | Tic Disorder, Unspecified F95.9 | Primary | MSH2 |
| Rosacea, Unspecified L71.9 | Secondary Carrier | AIRE |
| Dry Eye Syndrome H04.129 | Secondary Carrier | CFTR |
| Cerv Disc Disord M50.020 | Secondary Carrier | DMP1 |
| Raynaud’s Syndrome I73.00 | Secondary Carrier | FANCA |
| Hypothyroidism, Unspecified E03.9 | Secondary Carrier | MYBPC1 |
| Polyp of Colon K63.5 | | |
| Migraine G43.909 | | |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 33 | 67 | M | Hyperlipidemia, Unspecified E78.5 | Primary | LIPI |
| Circadial Rhythm Sleep Disord G47.20 | Secondary Disease | APC |
| Unspecified Hearing Loss H91.90 | Secondary Carrier | TUBGCP4 |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 34 | 67 | F | Hyperlipidemia, Unspecified E78.5 | Secondary Carrier | MEFV |
| Episodic Cluster Headache G44.019 | | |
| Essential (primary) Hypertension I10 | | |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 35 | 30 | M | Anxiety Disorder, Unspecified F41.9 | Secondary Carrier | LIG4 |
| Attention-Deficit Hyperactivity Disorder, Other Type F90.8 | | |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 36 | 74 | M | Polyneuropathy, unspecified G62.9 | Primary | COL11A2 |
| Essential Tremor G25.0 | Primary | SPTLC2 |
| Malignant Neoplasm of Prostate C61 | Secondary Carrier | SERPINA1 |
| Unspecified Sensorineural Hearing Loss H90.5 | Secondary Carrier | CEP104 |
| Other Seborrheic Keratosis L82.1 | | |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 37 | 68 | F | Malignant Neoplasm Of Unspecified Site Of Left Female Breast C50.912 | Primary | COL6A3 |
| Transient Cerebral Ischemic Attack, Unspecified G45.9 | Secondary Carrier | ACADM |
| 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 | | |
| Dvtclso Of Lg Int W/o Perforation Or Abscess W/o Bleeding K57.30 | | |
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 38 | 63 | M | Headache R51 | Primary | TET2 |
| Hyperlipidemia, Unspecified E78.5 | Secondary Carrier | GJB2 |
| VentricularPrematureDepolarizationI49.3 | Secondary Carrier | PKLR |
| Other Specified Anxiety Disorders F41.8 | Secondary Carrier | SLC6A19 |
| GERD K21.0 | Secondary Carrier | USH2A |
| 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 | | |
| Transcript   | Variant (genomic) | Variant (coding) | Variant (protein) | Variant classification |
|--------------|-------------------|------------------|-------------------|------------------------|
| NM_000251.2  | chr:2:g.47637301T>G | c.435T>G         | p.Ile145Met       | VUS                    |
| NM_000383    | chr21:g.45711063_45711075delG  | c.965_977delGCCTGCCCTCC | p.Leu323SerfsTer51 | Pathogenic             |
| NM_000492.3  | chr7:g.1117199645_111719964delTCT | 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_89828379insCAGCTCGAGGTGAAATTTC    | c.2830_2831dupGAAATTCAACC TGAAGCTG | 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_43675558insT | 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.94844947T>A  | c.1096G>A        | p.Glu366Lys       | Pathogenic             |
| NM_014704.3  | chr11:g.37504584delT | c.1627delC       | p.Arg543AlafsTer33 | Likely Pathogenic      |
| NM_004369.3  | chr2:g.238243533C>G   | c.8966-1G>C      | NA                | Pathogenic             |
| NM_000016.5  | chr1:g.762266846A>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)
| Participant information | Variant information |
|-------------------------|---------------------|
| **Insight number** | **ICD10** | **Variant category** | **Gene** |
| 39 | 62 | F | Fibromyalgia M79.7 | Secondary Carrier | COL18A1 |
| | | | Primary Hypertension I10 | Secondary Carrier | VWF |
| | | | Hyperlipidemia E78.5 | Secondary Disease | WNT10A |
| | | | Unspecified Osteoarthritis M19.90 | | |
| | | | GERD K21.0 | | |
| 40 | 89 | F | Idiopathic Pulmonary Fibrosis J84.112 | Secondary Carrier | ATP7B |
| | | | Hyperlipidemia E78.5 | Secondary Carrier | GJB2 |
| | | | Unspecified Osteoarthritis M19.90 | Secondary Carrier | PKLR |
| | | | Age-Related Cataract H25.9 | Secondary Carrier | SLC6A19 |
| | | | | Secondary Carrier | USH2A |
| 41 | 34 | M | Rhabdomyolysis M62.82 | Primary | ANOS |
| | | | Hemochromatosis E83.119 | Primary | HFE |
| | | | Abnormal Levels of Other Serum Enzymes R74.8 | Secondary Carrier | IDUA |
| | | | Pure Hypercholesterolemia E78.00 | Secondary Carrier | STARD9 |
| 42 | 88 | M | Unspecified Hearing Loss H91.90 | Primary | ABCA4 |
| | | | Angina Pectoris I20.9 | Primary | CDH23 |
| | | | Prediabetes R73.03 | Primary | HMCN1 |
| | | | Macular Degeneration H35.30 | Primary | THAP1 |
| | | | Age-Related Cataract H25.9 | Primary | THAP1 |
| | | | Unspecified Osteoarthritis M19.90 | Secondary Carrier | FANCA |
| | | | Family History of Carrier of Other Genetic Disease Z84.81 | Secondary Carrier | SERPINA1 |
| 43 | 72 | M | Parkinson's Disease G20 | Secondary Disease | BRCA2 |
| | | | Persisant Atrial Fibrillation I48.1 | Secondary Carrier | HFE |
| | | | Other Age-Related Cataract H25.89 | Secondary Carrier | MCPH1 |
| | | | | Secondary Disease | NLRP3 |
| | | | | Secondary Carrier | GNRHR |
| 44 | 52 | M | Hyperlipidemia, Unspecified E78.5 | Primary | STAP1 |
| | | | Gout, Unspecified M10.9 | Secondary Carrier | OCA2 |
| | | | Obstructive Sleep Apnea G47.33 | Secondary Carrier | ADAR |
| | | | | Secondary Carrier | PNPO |
| | | | | Pharmacogenetic | CYP2C9 |
| | | | | Pharmacogenetic | VKORC1 |
| | | | | Pharmacogenetic | CYP2C19 |
| | | | | Pharmacogenetic | CYP2D6 |
| 45 | 72 | M | Rheumatoid Arthritis, Unspecified M06.9 | Secondary Carrier | BCHE |
| | | | Calculus Of Kidney N20.0 | Secondary Carrier | FKBP14 |
| | | | Malignant Melanoma Of Skin, Unspecified C43.9 | Secondary Carrier | IRAK4 |
| | | | Unspecified Age-Related Cataract H25.9 | Secondary Carrier | LIPA |
| | | | Acute Myocardial Infarction, Unspecified I21.9 | Secondary Carrier | FLG2 |
| | | | | Secondary Carrier | IL17RA |
| | | | | Secondary Carrier | PEX6 |
| Transcript(s) | Participant Information | Variant Information | Insight |
|---------------|-------------------------|---------------------|---------|
| 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.--22A>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.21659590A>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.9816466C>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.Arg530Gln | VUS |
| NM_018105.2   | chr8:42694447T>C | c.149A>G | p.Tyr50Cys | VUS |
| NM_018105.2   | chr8:42694435G>A | c.161G>C | p.Cys54Ser | VUS |
| NM_000135.2   | chr16:89816189C>T | c.3188G>A | p.Trp1063Ter | Pathogenic |
| NM_002095.4   | 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.68424526G>A | 35G>A | R12H | VUS |
| NM_0000275    | chr15:g.28230247C>T | 1327G>A | V443I | Pathogenic |
| NM_015840     | chr1:g.154575451G>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   | chr12:41476108A>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 326321insTA | c.3940_3941dupTA | p.Trh1314LfsfsTer223 | Likely Pathogenic |
| NM_014339.6   | chr22:17566012_176 66013insT | c.31insT | p.Pro14AlafsTer42 | Likely Pathogenic |
| NM_000287.3   | chr6:42935188C>T | c.1802G>A | p.Arg601Gln | Likely Pathogenic |

(Continues)
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...
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).

| 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 7558insT | 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.Lys728AspsfsTer19 | Likely Pathogenic      |
| NM_000155.3 | chr9:34646576_346 6579delCAGT | c.−116_−116delGTCA | NA               | Likely Pathogenic      |
| NM_001015878.1 | chr19:57232070delIC | c.145delC      | p.Leu49TrpsfsTer23 | 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 | chr9:35092076_3509 2077insG | c.1810dupC | p.Arg604ProfsfsTer40 | 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 | chr14:118797796G>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      |

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.
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 untreated 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 \( \text{range 30–102} \).

### 3.2 Clinical genome sequencing results

Twenty-six primary results potentially related to clinical phenotype were identified in 18 of 52 participants \( \text{(four individuals received multiple findings)} \). 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 \( \text{(Kalai et al., 2017)} \) \( \text{(two in \text{APC} (*611731)}, \text{and one in \text{BRCA2} (*600185)} \). Eighty-five percent \( (n = 44) \) had a carrier status identified for at least one autosomal recessive or X-linked disorder \( \text{(range 1–7 variants, median 2 variants)} \). 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 \( \text{(Table 1)} \).

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

When compared to the variants found on the GSA \( \text{(Illumina)} \), 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 \( \text{(Table 2)} \).

### 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 \( \text{(Hou et al., 2020)} \).

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 \text{PRF1} \( (*170280) \). Autosomal recessive \text{PRF1}-associated hemophagocytic lymphohistiocytosis may present with lymphoma as the initial manifestation \( \text{(Tesi et al., 2016)} \). Interestingly, there is evidence that carriers of \text{PRF1} variants are at risk for lymphomas \( \text{(Chen et al., 2017; Ciambotti et al., 2014; Ding & Yang, 2013)} \). Digenic inheritance has also been suggested \( \text{(Clementi et al., 2004)} \). 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 \text{ANOS5} \( (*608662) \). While the second variant in \text{trans} was not identified, the patient's phenotype is consistent with the wide variability seen in \text{ANOS5} muscle disease \( \text{(Jarmula et al., 2019; Penttilä et al., 2012; Savarese et al., 2016)} \). Reports suggest that carriers of \text{ANOS5} variants may have a mild phenotype including cramps and increased CK \( \text{(Jarmula et al., 2019; Savarese et al., 2016)} \). Case 37 had episodic facial dystonia and was heterozygous for a c.8966-1G>C canonical splice site variant in \text{COL6A3} \( (*120250) \). The patient's phenotype resembles cases of autosomal recessive dystonia-27 \( \text{(DYT-27)} \), 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 \( \text{(Panda & Sharawat, 2020)} \). The variant reported in case 37 was seen in two \text{DYT-27} pedigrees \( \text{(Jochim et al., 2016; Zech et al., 2015)} \). Case 42 had age-related macular degeneration \( \text{(AMD)} \) and an established pathogenic \text{ABCA4} \( (*601691) \) variant c.3113C>T \( \text{(p. Ala1038Val)} \). \text{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 \( \text{(Cremers et al., 2020; Zernant et al., 2017)} \). In these cases, there are three potential explanations: (1) a second disease-causing variant is actually
| 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 | 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 |
| 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   | CYP2C19               | *2/*2xA      | Ultrarapid Metabolizer                |
|                |     |     | CYP2C19               | *1/*2         | Intermediate Metabolizer              |
|                |     |     | IFNL3                 | rs12979860T/T | Reduced Response to Hepatitis C Treatment |
|                |     |     | F5                    | F5 Leiden     | Increased Thrombophilia Risk          |
|                |     |     | COMT                  | Met/Met       | Reduced Stimulant Response            |
| 26             | 59  | M   | CYP2C19               | *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   |
| 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/*1    | 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                    |
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

| 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   |        | Slightly Reduced Stimulant Response |
| 47             | 58  | F   | CYP2C19 | *1/*17 | Rapid Metabolizer |
|                |     |     | IFNL3  | rs12979860 C/T | Reduced Response to Hepatitis C Treatment |
|                |     |     | F5     |        | Increased Thrombophilia Risk |
|                |     |     | COMT   |        | 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   |        | 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   |        | 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   |        | Slightly Reduced Stimulant Response |

TABLE 2 (Continued)
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.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the participants in this study, without whom this research, and the resulting information, would not have been possible.

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.

ORCID

David Bick @ https://orcid.org/0000-0002-8750-306X
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., Huilick, 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-Bisroiy, O., Mury, 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-Bisroiy, 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, 5249–5256. https://doi.org/10.3892/ol.2017.6898

Ciambritti, B., Massolin, L., D’Amore, E. S. G., Pillon, M., Sieni, E., Coniglio, M. L., Ros, M. D., Cetica, V., Aricò, M., & Rösolen, 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., Chiochetti, A., Sabbadini, M. G., Rugarli, C., Ciceri, F., Maccario, R., Locatelli, F., Danesino, C., Ferrari, 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 Penetration/Risk Allele Working Group. https://clinicalgenome.org/site/assets/files/4531/clinengrisk_terminology_recommendations-final-02_18_20.pdf

Cremers, F. P. M., Lee, W., Collin, R. W. J., & Allikmens, 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., Chab, H., Merker, J. D., Goldfeber, R. L., Enns, G. M., David, S. P., Pakdaman, N., Ormond, K. E., Caleshu, C., Kingston, 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., Abdul-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 DiscovEH 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.1924-0864.2013.02.008

Drost, M., Tiemers, Y., Glubb, D., Kathe, S., van Hees, S., Calléja, F., Zonneveld, J. B. M., Boucher, K. M., Ramal, 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-pathmedics-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 1-sirene 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). ASXL3 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., Jeromin, A., McKenna-Yasek, D., Walsh, K., Aziz-Bose, R., Oaklander, A. L., Brown, R., Hornemann, T., & Eichler, F. (2019). Randomized trial of 1-sirene in patients with hereditary sensory and autonomic neuropathy type 1. Neurology, 92(4), e359–e370. https://doi.org/10.1212/wnl.0000000000006811

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. Genetcs in Medicine, 23(7), 1255–1262. https://doi.org/10.1016/j.gim.2020.01.014

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., Bareja, 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://usdonalphal.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). ANOS 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., Gura-Stahlberg, G., Winkelmann, J., & Haslinger, B. (2016). The clinical phenotype of early-onset isolated dystonia caused by recessive COL6A3 mutations (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. L., & 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/10.1016/j.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). COL6A3 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., Lacerza, P., Rath, E. M., Stone, A., Brion, M.-J., Ameer, A., Nagpal, S., Puttic, 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, S., Dagan-Rosenfeld, O., Zhou, W., Sailani, M. R., Limcaoco, P., Pandey, A. K., Gongza-Jauregui, C., Khalid, S., Ye, B., Banerjee, N., Li, A. H., O’Dushlaine, C., Marcksetta, A., Staples, J., Schurmann, C., Hayes, 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, W., van der Linden, A., & Verkerk, A. J. (2020). Reduced penetrance of atherogenic ACMG variants in a deeply phenotyped cohort study and evaluation of ClinVar Classification over time. Genetics in Medicine, 22(11), 1812–1820.

Worthy, E. A. (2017). Analysis and annotation of whole-genome or whole-exome sequencing derived variants for clinical diagnosis. Current Protocols in Human Genetics, 95, 2.24.1–2.24.28.

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., & Winkelmans, J. (2015). Recessive mutations in the α3 (VI) collagen gene COL6A3 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 ABCA4 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.
APENDIX 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.