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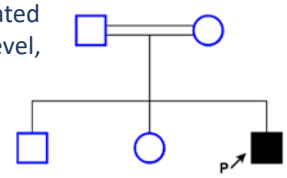
Add genetics to your health

Name: John Doe
Medical Request No. 1234567

D.O.B:	dd/mm/yyyy	Referring physician:	Dr. Doctor name
Sex:	Male	Referring facility:	Medical Center, Country
Subject ID:	8xxxx	Email physician:	doctorname@email.com
Order ID:	2xxxxx	Report type:	myLifeGenome
Device/ Material ID:	ARCxxxxxx	Date of report:	11/12/2023
Specimen type:	Buccal swab		
Specimen arrival date:	dd/mm/2023		

Requested Test: myLifeGenome
Indication for test: Elevated circulating alkaline phosphatase concentration, Elevated gamma-glutamyltransferase level, Increased circulating IgE level, Pancytopenia, Severe generalized osteoporosis



Consanguineous parents: Yes
Consent for evaluation: Primary findings: Yes
Incidental findings: Yes

SUMMARY OF GENETIC FINDINGS

PRIMARY	INCIDENTAL	CARRIER STATUS	PHARMACOGENOMICS
Positive	Negative	Positive	Positive

Primary Findings

ⓘ Primary findings describe genetic variants that are relevant to the indication for which sequencing was ordered.

Results: A homozygous likely pathogenic variant was identified in the SLC7A7 gene. This result is consistent with the genetic diagnosis of autosomal recessive lysinuric protein intolerance.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
SLC7A7	c.1429+1G>C; p.?	Hom	LP	Lysinuric protein intolerance	AR

Incidental Findings

ⓘ Incidental findings describe actionable variants in gene(s) that are unrelated to the indication for which sequencing was ordered. These findings are reported based on ACMG guidelines and ClinGen recommendations.

Results: No incidental finding detected.

Carrier Status

ⓘ Carrier Status includes pathogenic or likely pathogenic variants which have a direct impact on reproductive risk (heterozygous variants in a gene associated with a recessive or X-linked disorder).

AD: autosomal dominant, AR: autosomal recessive, Het: Heterozygous; Hom: Homozygous; LP: Likely Pathogenic; P: Pathogenic; RF: risk factor VUS: Variant of Uncertain Significance.

Results: This proband is found to be a carrier for 3 genetic conditions.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
TPRN	c.25delT; p.Ser9fs*22	Het	LP	Deafness type 79	AR
DHTKD1	c.1671+1G>A; p.?	Het	LP	Alpha-aminoadipic and alpha-ketoadipic aciduria	AR
CEP250	c.6913C>T; p.Arg2305*	Het	LP	Cone-rod dystrophy and hearing loss type 2	AR

Pharmacogenomic Associations

Pharmacogenomic (PGx) Associations are representations of the relationship between specific genes and drugs based on their drug metabolizing status defined according to publicly available data sets provided by Clinical Pharmacogenetics Implementation Consortium (CPIC) (mainly levels A/B or 1/2) using Pharmacogenomics Clinical Annotation Tool (PharmCAT).

Results: Genetic variants associated with drug use and dosing were identified.

See the Pharmacogenomic Associations section under Detailed Insights to understand the identified gene-drug pairs that could lead to treatment modifications based on the individual's genetic variants. See Technical Information section for the list of all genes and drugs supported by PharmCAT.

RECOMMENDATIONS

- Genetic counselling is recommended to further explain the implications of this test result and assess family health history, which may point to health information that merits additional consideration.
- The medical genetics field is continuously evolving, so updates related to your genetic results, medical recommendations, and potential treatments may be available over time.
- Lysinuric protein intolerance is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes (i.e. carriers). At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once pathogenic variants in the family are known, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing is possible. It is recommended to provide biological material from family members to identify at-risk carriers by Sanger sequencing.

Signatures

Medical Advisor | Lab Director | Clinical Genomics Scientist

DETAILED INSIGHTS

Primary Findings

A homozygous likely pathogenic variant was identified in the SLC7A7 gene. This result is consistent with the genetic diagnosis of autosomal recessive lysinuric protein intolerance.

SLC7A7 (Solute Carrier Family 7 Member 7) is a protein coding gene. The protein encoded by this gene is the light subunit of a cationic amino acid transporter. This sodium-independent transporter is formed when the light subunit encoded by this gene dimerizes with the heavy subunit transporter protein SLC3A2. This transporter is found in epithelial cell membranes where it transfers cationic and large neutral amino acids from the cell to the extracellular space. Alternative splicing results in multiple transcript variants.

	Gene/OMIM	*SLC7A7/603593*
	Genomic coordinate (GRCh38)	chr14:22773932C>G
	ID Transcript	NM_003982.4
	HGVS nomenclature	c.1429+1G>C
	Protein change	p.?
	Location	exon 9/10
	Zygosity	Hom
	Function	Splice site donor
	Impact	High
	ClinVar	N/A
Allele Frequency	Local Database	N/A
	gnomAD	N/A
In silico Predictors	REVEL	N/A
	CADD (PHRED)	33.0
	Splice-AI	0.94
	Clinical significance	likely pathogenic
	ACMG Criteria	PVS1, PM2

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; rages from 0 to 1)= higher scores reflect greater likelihood that variant is disease- causing; CADD (PHRED)= Combined Annotation Dependent Depletion scoring, ranging from 1 to 99, Splice-AI= deep neural network that accurately predicts splice junctions from an pre-mRNA transcript (using 0.8 as high-precision cut-off).
**: The ACMG criteria are described under Methods /Variant interpretation section.*

Disease description: Lysinuric protein intolerance (LPI) typically presents after an infant is weaned from breast milk or formula; variable findings include recurrent vomiting and episodes of diarrhea, episodes of stupor and coma after a protein-rich meal, poor feeding, aversion to protein-rich food, failure to thrive, hepatosplenomegaly, and muscular hypotonia. Over time, findings include: poor growth, osteoporosis, involvement of the lungs (progressive interstitial changes, pulmonary alveolar proteinosis) and of the kidneys (progressive glomerular and proximal tubular disease), hematologic abnormalities (normochromic or hypochromic anemia, leukopenia, thrombocytopenia, erythroblastophagocytosis in the bone marrow aspirate), and a clinical presentation resembling the hemophagocytic lymphohistiocytosis/macrophagic activation syndrome. Hypercholesterolemia, hypertriglyceridemia, and acute pancreatitis can also be seen.
In acute hyperammonemic crises, treatment of manifestations relies on intravenous administration of arginine chloride and nitrogen-scavenger drugs (sodium benzoate, sodium phenylacetate) to block ammonia production; reduction of excess nitrogen in the diet; provision of energy as carbohydrates to reduce catabolism. Long-term treatment is via dietary protein restriction; oral supplementation with citrulline and nitrogen-scavenger drugs, L-lysine-HCl, and carnitine; whole-lung lavage to improve respiratory function in persons with pulmonary alveolar proteinosis. Long-term protein restriction and administration of citrulline and nitrogen-scavenging drugs help to prevent primary manifestations. For prevention of secondary complications, minimizing the risk of respiratory infections by vaccination is recommended.
Individuals with Lysinuric protein intolerance may participate in clinical trials: https://clinicaltrials.gov/search?cond=LYSINURIC%20PROTEIN%20INTOLERANCE

Variant description: This variant is predicted to disrupt the highly conserved splicing site. The variant is absent in gnomAD and from the local database. This variant is not listed in ClinVar. This variant is classified as likely pathogenic based on ACMG recommendations.

Carrier Status Findings

Carrier status determines the proband's risk for passing inherited genetic condition(s) to the children. Carriers are typically healthy/ asymptomatic. When an individual is found to be a carrier of a genetic condition, his or her relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. If an individual is found to be a carrier of a specific condition, the patient's reproductive partner should be offered testing to receive informed genetic counseling about potential reproductive outcomes. If both partners are found to be carriers of a genetic condition, genetic counseling should be offered.

This proband is found to be a carrier for 3 genetic conditions.

Gene	Variant details	Zygosity	Annotations	Related disease (OMIM)- MOI Clinical assessment	Clinical significance (ACMG criteria*)
TPRN	chr9:137200686GA>G NM_001128228.3 c.25delT p.Ser9fs*22 Exon/Intron rank:1/4 Frameshift Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: N/A -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):N/A -Splice-AI:0.0	Deafness type 79 AR Carrier	Likely pathogenic PVS1, PM2
DHTKD1	chr10:12097997G>A NM_018706.7 c.1671+1G>A p.? Exon/Intron rank:8/17 Intron, Splice site donor Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: 0.0000167 -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):33.0 -Splice-AI:1.0	Alpha-aminoadipic and alpha-ketoadipic aciduria AR Carrier	Likely pathogenic PVS1, PM2
CEP250	chr20:35508949C>T NM_007186.6 c.6913C>T p.Arg2305* Exon/Intron rank:33/35 Nonsense Impact:High	Het	-ClinVar:N/A -Mastermind ID:N/A -gnomAD Total: N/A -Internal DB:N/A -Total MAF:N/A -REVEL:N/A -CADD (PHRED):48.0 -Splice-AI:0.21	Cone-rod dystrophy and hearing loss type 2 AR Carrier	Likely pathogenic PVS1, PM2

**: The ACMG criteria are described under Methods /Variant interpretation section.*

Pharmacogenomic Associations

This test identified the following variants associated with drug use and dosing generated based on PharmCAT v2.8 (according to CPIC Guidelines (https://cpicpgx.org/guidelines). Pharmacogenetic tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

Genetic variants associated with drug use and dosing were identified.

Drugs	PGx Phenotype	Genes / Genotype	CPIC recommendations
Acenocoumarol	Not assigned	VKORC1: rs9923231 reference (C)/ rs9923231 variant (T)	No CPIC recommendations available for this drug-gene interaction.
Allopurinol	Normal metabolizer	ABCG2: rs2231142 reference (G)/ rs2231142 reference (G)	No CPIC recommendations available for this drug-gene interaction.
Amitriptyline	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Atazanavir	Intermediate metabolizer	UGT1A1:*1/*80+*28	There is no need to avoid prescribing of atazanavir based on UGT1A1 genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient's genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).
Atorvastatin	Normal metabolizer	SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.
Azathioprine	Normal metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 2-3 mg/kg/day) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 11302950, 15606506).
Capecitabine	Not assigned	DPYD:c.1601G>A (*4) DPYD:c.1627A>G (*5)	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.
Celecoxib	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Citalopram	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Clomipramine	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Clopidogrel	Normal metabolizer	CYP2C19:*1/*1	If considering clopidogrel, use at standard dose (75 mg/day)
Dapsone	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Desflurane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Dexlansoprazole	Normal metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Doxepin	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Efavirenz	Normal metabolizer	CYP2B6:*1/*2	Initiate efavirenz with standard dosing (600 mg/day).
Enflurane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Escitalopram	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.

Flucytosine	Not assigned	DPYD:c.1601G>A (*4) DPYD:c.1627A>G (*5)	No CPIC recommendations available for this drug-gene interaction.
Fluorouracil	Not assigned	DPYD:c.1601G>A (*4) DPYD:c.1627A>G (*5)	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.
Flurbiprofen	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Fluvastatin	Normal metabolizer	CYP2C9:*1/*1 SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines.
Fosphenytoin	Normal metabolizer	CYP2C9:*1/*1	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN and patients should be carefully monitored according to a usual standard.
Halothane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Ibuprofen	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Imipramine	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Irinotecan	Intermediate metabolizer	UGT1A1:*1/*80+*28	No CPIC recommendations available for this drug-gene interaction.
Isoflurane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Ivacaftor	Ivacaftor non-responsive in cf patients	CFTR:Reference/ Reference	Ivacaftor is not recommended.
Lansoprazole	Normal metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Lornoxicam	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Lovastatin	Normal metabolizer	SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.
Meloxicam	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Mercaptopurine	Normal metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 75 mg/m2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents. Allow at least 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 16401827, 11302950).
Methoxyflurane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Methylene blue	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Nitrofurantoin	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Omeprazole	Normal metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and

			erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Pantoprazole	Normal metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Peginterferon alfa-2a	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Peginterferon alfa-2b	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Pegloticase	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Phenprocoumon	Not assigned	VKORC1: rs9923231 reference (C)/ rs9923231 variant (T)	No CPIC recommendations available for this drug-gene interaction.
Phenytoin	Normal metabolizer	CYP2C9:*1/*1	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN and patients should be carefully monitored according to a usual standard.
Piroxicam	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Pitavastatin	Normal metabolizer	SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.
Pravastatin	Normal metabolizer	SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.
Primaquine	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Quetiapine	Normal metabolizer	CYP3A4:*1/*1	No CPIC recommendations available for this drug-gene interaction.
Rasburicase	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Ribavirin	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Rosuvastatin	Normal metabolizer	ABCG2: rs2231142 reference (G)/ rs2231142 reference (G) SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines.
Sertraline	Normal metabolizer	CYP2B6:*1/*2 CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Sevoflurane	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Simvastatin	Normal metabolizer	SLCO1B1:*1/*14	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.
Siponimod	Normal metabolizer	CYP2C9:*1/*1	No CPIC recommendations available for this drug-gene interaction.
Succinylcholine	Uncertain susceptibility	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Tacrolimus	Poor metabolizer	CYP3A5:*3/*3	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.
Tafenoquine	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Tegafur	Not assigned	DPYD:c.1601G>A (*4) DPYD:c.1627A>G (*5)	No CPIC recommendations available for this drug-gene interaction.
Tenoxicam	Normal metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.

Thioguanine	Normal metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 40-60 mg/m2/day) and adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 11037857).
Toluidine blue	Normal metabolizer	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status.
Trimipramine	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Voriconazole	Normal metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended standard of care dosing.
Warfarin	Normal metabolizer	CYP2C9:*1/*1 CYP4F2:*1/*1 VKORC1: rs9923231 reference (C)/ rs9923231 variant (T) rs12777823:G/G	The updated guideline for pharmacogenetics-guided warfarin dosing is published by the *Clinical Pharmacogenetics Implementation Consortium*. The recommendations for dosing are for adult and pediatric patients that are specific to continental ancestry, and are based on genotypes from *CYP2C9, VKORC1, CYP4F2*, and rs12777823. For more information please visit: https://www.pharmgkb.org/guidelineAnnotation/PA166104949

TECHNICAL INFORMATION

Methods	**Whole genome sequencing and data analysis.** DNA was extracted from a biological sample and TruSeq Nano DNA High Throughput Library Prep Kit (Illumina®) was used to prepare libraries, which were sequenced using the 150nt pair-end protocol on an Illumina platform to yield an average coverage depth of 30x for the nuclear genome and at least 1000x for the mitochondrial genome. Bacterial contamination of a sample may impact the depth of coverage. Raw read alignment to reference genome GRCh38 and variant calling, including single nucleotide substitutions (SNVs), small insertions/deletions (Indels) and structural variants (SVs) with default parameters were performed using DRAGEN (version 4.2.4, Illumina). SNV and Indel variant annotation was performed by Geneyx (https://geneyx.com). Structural variants were annotated with ANNOTSV3.1 and in- house structural variant database to obtain allele frequencies. For the mitochondrial genome, variants with frequencies/heteroplasmy level ≥5% are detected. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org).
	Incidental genes: The gene panel is based on the ACMG (American College of Medical Genetics and Genomics) SF v.3.2 recommendations (https://www.gimjournal.org/article/S1098-3600(23)00879-1/fulltext). ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1.
	Variant interpretation: All candidate variants were evaluated with respect to their pathogenicity and causality significance, and these are categorized following ACMG guidelines (PMID: 25741868) and ClinGen recommendations (https://www.clinicalgenome.org). All variants are verified to have good quality, and only those variants with evidence for causing or contributing to disease are reported as primary findings. The variants are classified following the 5-tier classes: pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign and benign. Likely benign and benign variants are not reported. VUSs are classified as "strong variants of unclear significance" when there is limited supporting evidence for pathogenicity (e.g., rare or absent from general population databases BUT in silico tools predict a deleterious effect on the protein consistent with the mechanism of disease; AND the gene has already been confirmed to be associated with the patient's observed phenotype). Incidental findings that do not correlate with the provided phenotype(s) are reported according to ACMG recommendations for reporting of incidental findings in using clinical exome and genome sequencing (PMID: 37347242), if consented. Only variants classified as pathogenic, likely pathogenic or uncertain (variants of unknown significance or VUS) according to the ACMG guidelines and associated with the patient's phenotype are listed among the primary findings. Variants of uncertain significance are categorized as strong candidates when they extremely are very rare or absent in external and internal databases, are predicted to be deleterious, and the respective gene matches patient's phenotype (i.e. insufficient evidence available). Variants like risk factors (or risk alleles) and genetic modifiers, impacting the disease severity are reported ONLY when extensive scientific and clinical evidence is established. ACMG criteria for classifying pathogenic variants: PVS1- Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease; PS1- Same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2- De novo (both maternity and paternity confirmed) in a patient with the disease and no family history; PS3- Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product; PS4- The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls; PM1- Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation; PM2- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; PM3- For recessive disorders, detected in trans with a pathogenic variant; PM4-Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants; PM5- Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before at the acid/protein level; PM6- Assumed de novo, but without confirmation of paternity and maternity; PP1- Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease; PP2- Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease; PP3- Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc); PP4- Patient's phenotype or family history is highly specific for a disease with a single genetic etiology. ACMG criteria for classifying benign variants: BA1- Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; BS1- Allele frequency is greater than expected for the disorder; BS2- Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age; BS3- Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing; BS4- Lack of segregation in affected members of a family; BP1-

	Missense variant in a gene for which primarily truncating variants are known to cause disease; BP2- Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder; or observed in cis with a pathogenic variant in any inheritance pattern; BP3- In-frame deletions/insertions in a repetitive region without a known function; BP4- Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc); BP5- Variant found in a case with an alternate molecular basis for disease, BP7- A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved. **Consanguinity score (CS):** this score is obtained from the DRAGEN's region of homozygosity calculation that considers homozygous single nucleotide variants on the autosomes. The higher the score, the closer the biological relationship of subjects´ parents. A score above two (2) suggests consanguinity.
Pharmacogenomic variants	The design of the pharmacogenomics panel is based on PharmCAT v2.8.3 (https://pharmcat.org/) and CPIC v1.30.0 (https://cpicpgx.org/guidelines/). The list of genes and drugs covered by PharmCAT is provided under: https://pharmcat.org/Genes-Drugs The covered drugs based on Anatomical Therapeutic Chemical (ATC) classification by PharmCAT v2.8.3 are: i. Anti-cancer and immune response: Azathioprine, Capecitabine, Fluorouracil, Irinotecan, Mercaptopurine, Peginterferon alfa-2a, Peginterferon alfa-2b, Rasburicase, Siponimod, Tacrolimus, Tegafur, Thioguanine ii. Blood and cardiovascular system: Acenocoumarol, Atorvastatin, Clopidogrel, Fluvastatin, Lovastatin, Methylene blue, Phenprocoumon, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, Warfarin iii. Digestive system: Dexlansoprazole, Lansoprazole, Omeprazole, Pantoprazole iv. Infection control: Atazanavir, Dapsone, Efavirenz, Flucytosine, Nitrofurantoin, Primaquine, Ribavirin, Tafenoquine, Voriconazole v. Musculo-skeletal system: Allopurinol, Celecoxib, Flurbiprofen, Ibuprofen, Lornoxicam, Meloxicam, Pegloticase, Piroxicam, Succinylcholine, Tenoxicam vi. Nervous system: Amitriptyline, Citalopram, Clomipramine, Desflurane, Doxepin, Enflurane, Escitalopram, Fosphenytoin, Halothane, Imipramine, Isoflurane, Methoxyflurane, Phenytoin, Quetiapine, Sertraline, Sevoflurane, Trimipramine vii. Respiratory system: Ivacaftor viii. Other: Toluidine blue The covered genes by PharmCAT v2.8.3 are: ABCG2, CACNA1S, CFTR, CYP2B6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, CYP4F2, DPYD, G6PD, IFNL3, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC1 PharmCAT is only able to generate recommendations based on the information provided to the software. The gene and variant information for all reported sections are interpreted directly from Arcensus-supplied data. Reported genotype calls are displayed with respect to the reference genome. Variants indicated as homozygous or heterozygous differ from the GRCh38/hg38 reference sequence (wild type). For all genes, variation reported in the VCF file but NOT included in the gene definition table will not be considered during allele assignment. There is a possibility that any such variation results in a reduced or no activity allele which could lead to inaccurate phenotype and CPIC recommendation. Structural variation star alleles that cannot be detected using VCF file data: CYP2B7-CYP2B6 hybrids: CYP2B6*29, CYP2B6*30; Partial and whole gene deletions: CYP2C19*36, CYP2C19*37, CYP4F2*16, SLCO1B1*48, SLCO1B1*49. This test does not report polymorphisms other than those specifically listed, and mutations in other genes associated with drug metabolism will not be reported. All content is sourced from the CPIC database.
Limitations	The genetic result's interpretation is strongly dependent on the provided clinical information and family history. Misinterpretation may occur if this data is provided incorrectly or incompletely. Variant frequencies are subjected to changes due to growing variant databases and may result in reclassification of previously reported variants. The variants detected with this assay cover the whole genome, within (intragenic) and beyond (intergenic) genes. The detectable variant types include nucleotide substitution, small insertions/deletions, copy number variants (CNVs), inversions, translocations, and complex rearrangements. Variants may not be detected in low complexity genomic regions due to high sequence homology, pseudogenes, or highly repetitive sequences. This methodology detects events of mosaicism of single nucleotide variants (SVN) with an minor allele fraction of minimum of at least 10%. It is possible that a particular genetic variant may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the biological function of the gene and/or the impact of the variant on the expression and/or function of the gene.

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1kGenome:2019-02	ACMG:2023-10	CADD:1.6	ClinGen:2023-10	ClinVar:2023-10
Cytogenetic:2022-12	DbNsfp:4.4a	DbscSNV:1.1	DbSnp:1405	DGVGold:v107_2016-05-15
DGVSV:v107_2020-02-25	ESP6500:2	GeneEnhancerSv:v5.15	GeneyxRepeats:v1.1	Gerp:2010
gnomAD-exomes:2.1.1	gnomAD-genomes:3.1.2	gnomAD-mit:2.1.1	GnomADSV:v2.1	LitVar2:2023-10
MANE:v1.1				

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