HEALTH NUCLEUS™

Genomic Clinical Report

PATIENT INFORMATION

PATIENT NAME: Patient, Sample

MRN:	SEX:	DOB:
MRN-1234	Male	02/14/1959

ACCESSION #: Sample_Report_v5_0_A

TEST REQUESTED:	COLLECTION DATE:	ORDERING PROVIDER:
Genomic Clinical Report	07/25/2014	Physician Ordering

SAMPLE TYPE:	INDICATION:	SPECIMEN ID:
Whole blood sample	Healthy adult screening	1234567

REVIEW STATUS: FINAL

Hereditary Disease Risk

The scope of this section includes variants that, when found by themselves, are associated with high and moderate genetic risk of developing a disease. Depending on a variant zygosity and disease inheritance, the disease can affect you or represent a risk for the next generation (carrier variants).

FINDINGS SUMMARY

GENOME SUMMARY	
2.75 BILLION	Base pairs analyzed (94% of genome)
4.1 MILLION	Total variants detected
1498	Total genes assessed
1624	Total diseases assessed

YOUR RISK

YOUR DISEASE RISK	VARIANTS
Cardiovascular Disorder	1

YOUR CARRIER VARIANTS	VARIANTS
Liver Disorder	1

Variant Summary

HEALTH CATEGORY	GENE	VARIANT	ZYGOSITY	CLASSIFICATION	DISEASE ASSOCIATED	INHERITANCE
CARDIOVASCULAR DISORDER	*LDLR*	c.1747C>T (p.His583Tyr) NM_000527.4	Heterozygous	Likely pathogenic	Familial hypercholesterolemia	Autosomal dominant
LIVER DISORDER (CARRIER)	*UGT1A1*	c.1091C>T (p.Pro364Leu) NM_000463.2	Heterozygous	Likely pathogenic	Crigler-Najjar syndrome, type I; Gilbert syndrome	Autosomal recessive

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Variant Details

Variants Associated with Risk for Cardiovascular Disorder

+	LDLR likely pathogenic variant, c.1747C>T (p.His583Tyr)	Allele Frequency: 0.1272% (gnomAD, East Asian)

Patient was found to have a likely pathogenic variant associated with an increased risk for a Cardiovascular Disorder

The c.1747C>T variant has been identified in several unrelated individuals affected with familial hypercholesterolemia in heterozygous, homozygous, or compound heterozygous state (PMID 7903864, PMID 23155708, PMID 27206935). The c.1747C>T variant is one of the most frequent variants associated with familial hypercholesterolemia in Southeast China, Hong Kong, and Taiwan (PMID 22353362, PMID 27206935). The variant has also been observed in compound heterozygous state in individuals affected by skin xanthomas (PMID 23155708). Results from functional studies indicate that the c.1747C>T variant leads to impaired lipoprotein uptake by reducing the number of surface receptors (PMID 7903864, PMID 21511053).

The LDLR gene codes for a protein called low-density lipoprotein receptor. Low-density lipoprotein receptors play a critical role in regulating the amount of cholesterol in the blood by binding to particles called low-density lipoproteins (LDLs). These LDL particles are the primary carriers of cholesterol in the blood. Pathogenic LDLR variants are associated with autosomal dominant familial hypercholesterolemia (MIM 143890). Some of these pathogenic variants reduce the number of low-density lipoprotein receptors produced within cells, whereas, other ones disrupt the receptor's ability to remove low-density lipoproteins from the blood. Familial hypercholesterolemia is characterized by extremely high LDL cholesterol levels or total cholesterol levels associated with atherosclerotic plaque deposits and increased risk of coronary artery disease at an early age (PMID 2912433). The prevalence of familial hypercholesterolemia is between 1 in 200 and 1 in 250 individuals, and pathogenic LDLR variants contribute to about 80% of the familial hypercholesterolemia cases (PMID 24404629).

Variants Associated with Liver Disorder

+	UGT1A1 likely pathogenic variant, c.1091C>T (p.Pro364Leu)	Allele Frequency: 2.4272% (1000 Genomes, East Asian)

Patient is a carrier for a likely pathogenic variant associated with a Liver Disorder. Reproductive partner and/or first degree relatives may benefit from screening.

The UGT1A1 gene codes for an enzyme called UDP-glucuronosyltransferase 1-1, also known as UGT11 or bilirubin-specific UDPGT isozyme 1. The UGT1A1 enzyme glucuronidates bilirubin, a byproduct of red blood cell breakdown. UGT1A1 converts the toxic form of bilirubin to its nontoxic form, so that it can be removed

from the body. Pathogenic UGT1A1 variants are associated with autosomal recessive Gilbert syndrome (MIM 143500) and Crigler-Najjar syndrome (MIM 218800, MIM 606785). Individuals with Gilbert syndrome have approximately 30 percent of normal UGT1A1 enzyme function. As a result, unconjugated bilirubin is not glucuronidated quickly enough, and it builds up in the body, causing mild hyperbilirubinemia. Pathogenic UGT1A1 variants that cause Crigler-Najjar syndrome result in reduced or absent function of the UGT1A1 enzyme. Individuals with Crigler-Najjar syndrome type 1 (CN1) have no enzyme function, while individuals with Crigler-Najjar syndrome type 2 (CN2) have less than 20 percent of the normal function. The signs and symptoms of CN1 are more severe than those of CN2. The loss of UGT1A1 function decreases glucuronidation of unconjugated bilirubin leading to a build-up in the body, causing hyperbilirubinemia, jaundice, and sometimes kernicterus (PMID 12983120, PMID 1749222). The prevalence of CN1 and CN2 is unknown (ORPHA79234, ORPHA 79235).

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Pharmacogenomic Findings

The results of this section may help your doctor better understand how you process certain medications. The way you respond to drugs depends on genetics as well as other factors. Your doctor will take these factors into account when deciding which drug or what drug dose is the best for you. Do not stop taking or alter the dosage of any prescribed medications without consulting with your doctor beforehand.

FINDINGS SUMMARY

REPORTING SCOPE	
246	Total variants assessed
63	Total drugs assessed

YOUR RISK	
	**YOUR PHARMACOGENOMIC RESULTS**
	29 drugs potentially impacted

Drugs Potentially Impacted

THERAPEUTIC	GENE	GENOTYPE	PHENOTYPE	DRUG	COMMENTS
ANTIARRYTHMIC	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Propafenone (Rythmol®)	Increased risk of reduced efficacy due to lower plasma concentration of propafenone. Dose increase and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (DPWG guideline, PMID 11471772, PMID 18167502).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Amitriptyline (Elavil®)	Increased risk of reduced efficacy due to lower plasma concentration of amitriptyline. Dose increase, dose titration and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Clomipramine (Anafranil®)	Increased risk of reduced efficacy due to lower plasma concentration of clomipramine. Dose increase, dose titration and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).

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THERAPEUTIC	GENE	GENOTYPE	PHENOTYPE	DRUG	COMMENTS
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Desipramine (Norpramin®)	Increased risk of reduced efficacy due to lower plasma concentration of desipramine. Dose increase and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Doxepin (Silenor®)	Increased risk of reduced efficacy due to lower plasma concentration of doxepin. Dose increase and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Imipramine (Tofranil®)	Increased risk of reduced efficacy due to lower plasma concentration of imipramine. Dose increase, dose titration and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Nortriptyline (Pamelor®)	Increased risk of reduced efficacy due to lower plasma concentration of nortriptyline. Dose increase, dose titration and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Trimipramine (Surmontil®)	Increased risk of reduced efficacy due to lower plasma concentration of trimipramine. Dose increase, dose titration and drug monitoring are recommended. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Venlafaxine (Effexor®)	Increased risk of reduced efficacy due to lower plasma concentration of venlafaxine. Dose increase is recommended. Alternative medications (e.g., citalopram, sertraline) could be considered (FDA drug label, DPWG guideline).
ANTIDEPRESSANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Vortioxetine (Trintellix®)	Increased risk of reduced efficacy due to lower plasma concentration of vortioxetine. Dose increase is recommended (EMA drug label, PMID 24766668).
ANTIEMETIC AND ANTINAUSEANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Ondansetron (Zofran®)	Increased risk of reduced efficacy due to lower plasma concentration of ondansetron. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline, PMID 21596874).

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ANTIEMETIC AND ANTINAUSEANT	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Tropisetron (Navoban®)	Increased risk of reduced efficacy due to lower plasma concentration of tropisetron. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline, PMID 12728290).
ANTIFUNGAL	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Voriconazole (Vfend®)	Increased risk of reduced efficacy due to lower plasma concentration of voriconazole. Medications that are not predominantly metabolized by CYP2C19 should be considered (CPIC guideline).
BLOOD THINNER	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Clopidogrel (Plavix®)	Increased risk of bleeding due to increased platelet inhibition and decreased residual platelet aggregation. Use as directed (CPIC guideline).
BLOOD THINNER	*CYP2C9*	*1|*1	Normal Metabolizer	Warfarin (Coumadin®)	Calculation of warfarin dose based on combination of VKORC1 and CYP2C9 genotypes is recommended as described (FDA drug label, CPIC guideline).
BLOOD THINNER	*VKORC1*	no reportable mutations found	-	Warfarin (Coumadin®)	Individuals with rs9923231:CC generally have normal sensitivity to warfarin. Calculation of warfarin dose based on combination of VKORC1 and CYP2C9 genotypes is recommended as described (FDA drug label, CPIC guideline).
INVOLUNTARY MOVEMENT REDUCER	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Tetrabenazine (Xenazine®)	Increased risk of reduced efficacy due to lower plasma concentration of active metabolites of tetrabenzine. Dose increase and dose titration are recommended (FDA drug label, PMID 23280482).
OPIOID	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Codeine (Codeine Sulfate®)	Increased risk of severe or life-threatening drug toxicity (e.g., respiratory depression) and overdose (signs include extreme sleepiness, confusion, or shallow breathing) due to higher plasma concentration of morphine, an active metabolite of codeine. Avoid codeine use. Medications that are not predominantly metabolized by CYP2D6 (e.g., acetaminophen, NSAID, morphine not tramadol or oxycodone) should be considered (CPIC guideline, DPWG guideline).
OPIOID	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Oxycodone (Oxaydo®)	Increased risk of side effects (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) due to higher plasma concentration of oxycodone. Use as directed. Medications that are not predominantly metabolized by CYP2D6 (not tramadol or codein) should be considered (DPWG guideline, PMID 21735164).

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OPIOID	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Tramadol (Ultram®)	Increased risk of side effects (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) due to higher plasma concentration of active metabolites of tramadol. Dose reduction is recommended (DPWG guideline, PMID 18204346).
PROTON-PUMP INHIBITOR	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Esomeprazole (Nexium®)	Increased risk of reduced efficacy due to lower plasma concentration of esomeprazole. Dose increase is recommended (DPWG guideline, PMID 22324425).
PROTON-PUMP INHIBITOR	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Lansoprazole (Prevacid®)	Increased risk of reduced efficacy due to lower plasma concentration of lansoprazole. Dose increase is recommended (DPWG guideline).
PROTON-PUMP INHIBITOR	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Omeprazole (Prilosec®)	Increased risk of reduced efficacy due to lower plasma concentration of omeprazole. Dose increase is recommended (DPWG guideline).
PROTON-PUMP INHIBITOR	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Pantoprazole (Protonix®)	Increased risk of reduced efficacy due to lower plasma concentration of pantoprazole. Dose increase is recommended (DPWG guideline).
SSRI	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Citalopram (Celexa®)	Increased risk of reduced efficacy due to lower plasma concentration of citalopram. Medications that are not predominantly metabolized by CYP2C19 should be considered (CPIC guideline).
SSRI	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Escitalopram (Lexapro®)	Increased risk of reduced efficacy due to lower plasma concentration of escitalopram. Medications that are not predominantly metabolized by CYP2C19 should be considered (CPIC guideline).
SSRI	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Paroxetine (Paxil®)	Increased risk of reduced efficacy due to lower plasma concentration of paroxetine. Medications that are not predominantly metabolized by CYP2D6 should be considered (CPIC guideline).
SSRI	*CYP2C19*	*17|*17	Ultrarapid Metabolizer	Sertraline (Zoloft®)	Increased risk of reduced efficacy due to lower plasma concentration of sertraline. Use as directed. Medications that are not predominantly metabolized by CYP2C19 could be considered (CPIC guideline).
SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR	*CYP2D6*	*2x2|*29	Ultrarapid Metabolizer	Atomoxetine (Strattera®)	Increased risk of reduced efficacy due to lower plasma concentration of atomoxetine. Use as directed. Medications that are not predominantly metabolized by CYP2D6 could be considered (DPWG guideline, PMID 25919121).

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THERAPEUTIC	GENE	GENOTYPE	PHENOTYPE	DRUG	COMMENTS
STATIN	*SLCO1B1*	*15|*1B	Decreased Function	Simvastatin (Zocor®)	Increased risk of side effects (myopathy). Dose reduction, use of an alternative statin (e.g., pravastatin or rosuvastatin) and routine surveillance of the creatine kinase level are recommended (CPIC guideline).

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Gene and Phenotype Findings

GENE	GENOTYPE	PHENOTYPE	DRUGS
CYP2C19	*17|*17	Ultrarapid Metabolizer	Citalopram (Celexa®), Clobazam (Onfi®), Clopidogrel (Plavix®), Dexlansoprazole (Dexilant®), Diazepam (Valium®), Escitalopram (Lexapro®), Esomeprazole (Nexium®), Lansoprazole (Prevacid®), Omeprazole (Prilosec®), Pantoprazole (Protonix®), Rabeprazole (AcipHex®), Sertraline (Zoloft®), Voriconazole (Vfend®)
CYP2C9	*1|*1	Normal Metabolizer	Celecoxib (Celebrex®), Warfarin (Coumadin®)
CYP2D6	*2x2|*29	Ultrarapid Metabolizer	Amitriptyline (Elavil®), Aripiprazole (Abilify®), Atomoxetine (Strattera®), Carvedilol (Coreg®), Clomipramine (Anafranil®), Clozapine (Clozaril®), Codeine (Codeine Sulfate®), Desipramine (Norpramin®), Doxepin (Silenor®), Fluvoxamine (Luvox®), Imipramine (Tofranil®), Nortriptyline (Pamelor®), Ondansetron (Zofran®), Oxycodone (Oxaydo®), Paroxetine (Paxil®), Pimozide (Orap®), Propafenone (Rythmol®), Tamsulosin (Flomax®), Tetrabenazine (Xenazine®), Thioridazine (Mellaril®), Tolterodine (Detrol®), Tramadol (Ultram®), Trimipramine (Surmontil®), Tropisetron (Navoban®), Venlafaxine (Effexor®), Vortioxetine (Trintellix®)
DPYD	*1|*9A	Normal Metabolizer	Capecitabine (Xeloda®), Fluorouracil (Efudex®), Tegafur (UFT®)
G6PD	no reportable mutations found	-	Chloroquine (Aralen®), Chlorpropamide (Diabinese®), Dapsone (Aczone®), Glimepiride (Amaryl®), Glipizide (Glucotrol®), Methylene blue (Provayblue®), Nalidixic acid (NegGram®), Nitrofurantoin (Macrobid®), Norfloxacin (Noroxin®), Primaquine (Primaquine Phosphate®), Probenecid (Benemid®), Quinine (Qualaquin®), Rasburicase (Elitek®), Sulfasalazine (Azulfidine®)
POLG	no reportable mutations found	-	Valproic acid (Valproic®)
SLCO1B1	*15|*1B	Decreased Function	Simvastatin (Zocor®)
TPMT	*1|*1S	Normal Metabolizer	Azathioprine (Imuran®), Mercaptopurine (Purinethol®), Thioguanine (Tabloid®)
VKORC1	no reportable mutations found	-	Warfarin (Coumadin®)

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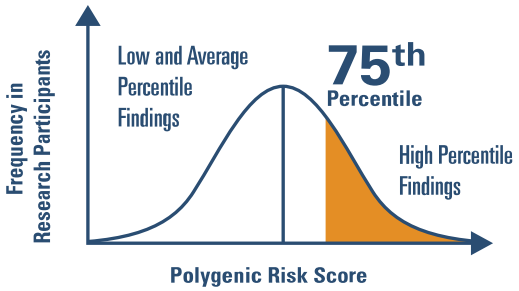
Health Predisposition

This section describes your genetic predisposition to common diseases using an innovative approach called polygenic risk scores. This approach identifies common variants you have that are associated with low genetic risk. Having several low risk variants related to the same disease predisposes you to that disease. Learn more in https://www.humanlongevity.com/your-results-guide-5-0.pdf.

Results use: The results in this section should not be used to guide medical care but rather to inform your lifestyle decisions. If you have a polygenic risk score that falls at or above the 75th percentile, it does not mean that you will develop the disease, rather it means that your genetic predisposition is increased. Lifestyle and environmental factors contribute more than genetics to the majority of common diseases. Polygenic risk scores in this report were developed using genomes of people of European descent and may be less accurate for people of other ethnicities.



High Percentile Findings (75th and above)

DISEASE	YOUR RESULT	ABOUT THE DISEASE
BLADDER CANCER	**Given the variants you have, your genetic predisposition to bladder cancer is greater than 91% of the research participants of European descent.**	- It is unknown how much genes contribute to the risk of bladder cancer. The research is underway. - Bladder cancer is a common disease; one in 27 men and one in 89 women will develop bladder cancer during their lifetime.

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DISEASE	YOUR RESULT	ABOUT THE DISEASE
COPD	Given the variants you have, your genetic predisposition to COPD is greater than 86% of the research participants of European descent.	- Genes contribute up to 60% to the risk of COPD. - COPD is a very common disease; one in five people 55 years or older will develop the condition during their lifetime.
CHRONIC LYMPHOCYTIC LEUKEMIA	Given the variants you have, your genetic predisposition to chronic lymphocytic leukemia is greater than 87% of the research participants of European descent.	- Genes contribute about 20% to the risk of developing chronic lymphocytic leukemia. - Chronic lymphocytic leukemia is a rare disease; one in 175 people will develop the condition during their lifetime.
GOUT	Given the variants you have, your genetic predisposition to gout is greater than 89% of the research participants of European descent.	- Genes contribute up to 60% to the risk of gout. - Gout is a common disease; one in 50 people will develop the condition during their lifetime.
INFLAMMATORY BOWEL DISEASE	Given the variants you have, your genetic predisposition to inflammatory bowel disease is greater than 88% of the research participants of European descent.	- Genes contribute up to 70% to the risk of inflammatory bowel disease. - Inflammatory bowel disease is common; one in 80 adults will develop either ulcerative colitis or Crohn's disease in their lifetime.
INSOMNIA	Given the variants you have, your genetic predisposition to insomnia is greater than 83% of the research participants of European descent.	- Genes contribute about 30 - 60% to the risk of developing insomnia. - Insomnia is a very common disorder; one in 10 adults and one in five elderly people are affected by the condition.
OSTEOPOROSIS	Given the variants you have, your genetic predisposition to osteoporosis is greater than 100% of the research participants of European descent.	- Genes contribute about 60 - 90% to the risk of osteoporosis. - Osteoporosis is a very common disease; one in three women and one in five men 50 years or older will have fractures due to osteoporosis during their lifetime.
RENAL CELL CARCINOMA	Given the variants you have, your genetic predisposition to renal cell carcinoma is greater than 92% of the research participants of European descent.	- Genes contribute about 40% to the risk of kidney cancer. - Renal cell carcinoma is a common disease; one in 48 men and one in 83 women will develop some type of kidney cancer during their lifetime.

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DISEASE	YOUR RESULT	ABOUT THE DISEASE
TYPE 2 DIABETES	**Given the variants you have, your genetic predisposition to type 2 diabetes is greater than 86% of the research participants of European descent.**	- Genes contribute about 70% to the risk of type 2 diabetes. - Type 2 diabetes is a very common disease; two out of five people will develop the condition during their lifetime.

Low and Average Percentile Findings (below 75th)

HEALTH CATEGORY	DISEASE (YOUR PERCENTILE)
CANCER PREDISPOSITION	Basal Cell Carcinoma (31th), Colorectal Cancer (4th), Esophageal Cancer (73th), Melanoma (13th), Pancreatic Cancer (16th), Thyroid Cancer (2th)
DIGESTIVE HEALTH	Celiac Disease (63th)
SENSORY HEALTH	Age-Related Macular Degeneration (40th), Nearsightedness (39th)
HEART AND VASCULAR HEALTH	Atrial Fibrillation (23th), Coronary Artery Disease (29th), Stroke (17th), Venous Thromboembolism (41th)
METABOLIC HEALTH	HDL Cholesterol (12th), Kidney Stones (8th), LDL Cholesterol (11th), Total Cholesterol (1th), Triglycerides (20th)
NEUROLOGICAL HEALTH	Alzheimer's Disease (11th), Multiple Sclerosis (5th), Parkinson's Disease (29th)
MUSCULOSKELETAL HEALTH	Dupuytren's disease (18th), Rheumatoid Arthritis (67th)
MENTAL HEALTH	Bipolar Disorder (21th), Schizophrenia (2th)
RESPIRATORY HEALTH	Asthma (37th), Asthma (43th)

Please refer to https://www.humanlongevity.com/your-results-guide-5-0.pdf for frequently asked questions, information on how each polygenic risk score was developed, and references supporting disease information in this section.

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Nutrition and Wellness Traits

This section describes how your genes affect your body's response to certain foods, exercise, as well as your habits. The research into genetics of some traits is ongoing. You will see an icon describing the level of scientific evidence next to each prediction – from preliminary (one star) to established (four stars). The results in this section should not be used to guide medical care but rather to inform your lifestyle decisions.

Nutrition

Vitamin A

Scientific Strength

YOUR RESULT	YOUR GENOTYPE
You are not at higher risk of vitamin A deficiency	BCMO1, rs7501331, CC
You are not at higher risk of vitamin A deficiency	BCMO1, rs12934922, AA

DESCRIPTION

Vitamin A is a group of fat-soluble micronutrients that are important for multiple functions including the maintenance of the immune system and good vision. Vitamin A in the body is primarily derived from beta-carotene, a compound found in many vegetables including carrots, spinach, and sweet potatoes. Genetic variants in the BCMO1 gene have been shown to be associated with an impaired conversion of beta-carotene into vitamin A. Certain genotypes are associated with a higher risk of vitamin A deficiency while other genotypes are not associated with higher risk. Preformed vitamin A supplements may help maintain healthy vitamin A levels in individuals who have a genetic predisposition to vitamin A deficiency.

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Vitamin B6

Scientific Strength

YOUR RESULT

You are likely to have a decreased vitamin B6 level

YOUR GENOTYPE

NBPF3, rs4654748, CT

DESCRIPTION

Vitamin B6 helps support your body's nervous system, promotes red blood cell health and is involved in sugar metabolism. Certain genotypes are likely to have lower levels of vitamin B6 while other genotypes are associated with typical levels of vitamin B6. Getting vitamin B6 from dietary sources such as whole grains, beans, fish, meat, eggs, and some cereals can help maintain healthy vitamin B6 levels.

Vitamin D

Scientific Strength

YOUR RESULT

You are more susceptible to developing vitamin D deficiency

YOUR GENOTYPE

GC, rs2282679, TG

You are more susceptible to developing vitamin D deficiency

GC, rs1155563, TC

DESCRIPTION

Vitamin D is an important micronutrient that is necessary for building and maintaining healthy bones. Vitamin D is made primarily in the skin after exposure to sunlight. Insufficient vitamin D levels may lead to thin and brittle bones as well as certain types of cancer. Certain genotypes make you at higher risk for vitamin D deficiency while other genotypes are associated with the typical risk of vitamin D deficiency. Getting vitamin D from dietary sources such as fish oil, fatty fish, fortified cereals, milk, and certain supplements can help maintain healthy vitamin D levels.

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Food Reactions

Alcohol Flush Reaction

YOUR RESULT

You are unlikely to flush after consuming alcohol

YOUR GENOTYPE

ALDH2, rs671, GG

DESCRIPTION

The alcohol flush reaction is experienced by some people after consuming alcohol. In these individuals, a toxic substance called acetaldehyde builds up after drinking and causes tiny blood vessels in the face to temporarily expand and fill with more blood, similar to blushing. It can also cause dizziness, headaches, and nausea. Certain genotypes may make you more prone to flushing after alcohol consumption while other genotypes carry a typical risk of flushing. Individuals who are more prone to flushing often avoid alcohol because the reaction is so unpleasant.

Caffeine Metabolism

YOUR RESULT

You are likely to metabolize caffeine more quickly, causing shorter stimulant effects

YOUR GENOTYPE

CYP1A2, rs762551, AA

DESCRIPTION

Caffeine is one of the most widely consumed stimulants in the world. Caffeine can be found in coffee, tea, soft drinks as well as included in some pain relievers and other medications. Individuals who are slow metabolizers may experience the stimulant effects of caffeine longer than individuals who are fast metabolizers. In addition to genetics, ability to metabolize caffeine can be affected by lifestyle choices such as smoking and overall caffeine consumption.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

Bitter Taste Perception

YOUR RESULT

You may be unable to detect bitterness in some foods

YOUR GENOTYPE

TAS2R38, rs713598, CC

DESCRIPTION

People have different sensitivities to taste. Genetic variants in the taste receptor gene TAS2R38 have been shown to influence the sensitivity to the bitter-tasting compound phenylthiocarbamide. The variants can partially explain the increased sensitivity to the bitter flavors found in some foods such as broccoli, brussels sprouts, grapefruit, cabbage, and coffee. Certain genotypes may make you more sensitive to bitter flavors, while other genotypes make you less sensitive to bitter flavors. People with increased sensitivity to bitter taste should be mindful of their salt intake since they tend to add excessive salt to mask the bitter flavor in their foods.

Sweet Taste

YOUR RESULT

You are likely to have a moderately reduced sensitivity to sweet foods, which could result in slightly higher sugar intake

You are likely to have typical sensitivity to sweet foods

YOUR GENOTYPE

TAS1R2, rs12033832, GA

TAS1R3, rs307355, CC

DESCRIPTION

Sweetness is one of the basic tastes among sour, salty, bitter, and umami. Humans are able to taste food and other substances with the tongue papillae, each consisting of hundreds of taste buds. Sweet taste perception in humans is mediated by the TAS1R2 and TAS1R3 genes. Depending on your genotype, you may have typical sensitivity, moderately reduced sensitivity, or reduced sensitivity to sweet foods. If you have moderately reduced or reduced sensitivity, you may prefer foods with more sugar.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

Fitness and Exercise

Achilles Tendinopathy

YOUR RESULT

You are likely at increased risk for an Achilles tendon injury or inflammation

YOUR GENOTYPE

GDF5, rs143383, AA

DESCRIPTION

The Achilles tendon, the thickest tendon in the human body, connects the calf muscles to the heel bone. Continued intense stress on the Achilles tendon, especially activities that involve running and jumping, can cause small breaks and tears (tendinopathy). Certain genotypes may make you more prone to injury while other genotypes have a typical risk of Achilles tendon injuries. You can help prevent Achilles tendon injuries by good stretching, maintaining a healthy weight, and avoiding certain medications like fluoroquinolones.

Insulin Sensitivity

YOUR RESULT

You are likely to have improved insulin sensitivity with exercise which allows your body to better process sugar

YOUR GENOTYPE

LIPC, rs1800588, CC

DESCRIPTION

Insulin is a hormone that allows your cells to use glucose or sugar. Individuals affected with type 2 diabetes do not respond well to insulin (insulin resistance) and, therefore, their sugar levels are high. Physical exercise is a beneficial way for affected individuals to increase sensitivity to insulin. Certain genotypes are likely to have improved insulin sensitivity with exercise, while others don't have as much improvement. Other ways to improve your insulin sensitivity include eating less simple carbohydrates, intermittent fasting, getting better sleep, and certain prescription medications.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

Muscle Performance

Scientific Strength

YOUR RESULT

You have a mix of fast twitch and slow twitch muscle type which gives you a modest benefit in power sports

YOUR GENOTYPE

ACTN3, rs1815739, CT

DESCRIPTION

Athletic performance is influenced by a large number of genetic and environmental factors. A genetic variant influences how much of the ACTN3 protein our body can produce or whether it can produce the protein at all. The ACTN3 protein is present in the fast-twitch muscle fibers responsible for generating force at high velocity, and is found in sprint and power-oriented athletes. Certain genotypes increase the likelihood of you having enhanced performance in power sports while individuals with mixed fast twitch/slow twitch fiber types have only a modest benefit in power sports. You can increase your fast twitch muscle fibers by doing certain sprint exercises and plyometrics.

Endurance Training

Scientific Strength

YOUR RESULT

You are likely to have typical performance as an endurance athlete

You are likely to have typical performance as an endurance athlete

YOUR GENOTYPE

ACTN3, rs1815739, CT

ACE, rs4343, GA

DESCRIPTION

Endurance training refers to exercise done for medium to longer duration at moderate intensity. Endurance training has multiple health benefits including positive impact on cholesterol levels, body fat, and insulin sensitivity. Certain genotypes are associated with enhanced endurance performance while other genotypes are associated with typical endurance performance. Improving endurance potential and stamina can be achieved by introducing variety into your workout routines, eating a balanced diet, and improving sleep.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

Behavior and Mood

Risk Seeking Behavior

YOUR RESULT

You are likely to have typical risk seeking behavior

YOUR GENOTYPE

DRD4, rs1800955, TC

DESCRIPTION

Human behavior is the result of a very complex interplay of environmental and biological factors. However, twin studies have shown that individual variation in sensation seeking is heritable, with few differences between males and females. The individual differences in risk taking behaviors can be partially explained by the variants in two genes, 5-HTTLPR and DRD4, that regulate dopamine and serotonin neurotransmission. These genes have been previously linked to emotional behavior, anxiety, and addiction. Certain genotypes are likely to have increased risk seeking behavior while other genotypes are associated with typical risk seeking behavior.

Smoking Behavior

YOUR RESULT

If you smoke, you are likely to smoke two more cigarettes per day on average than the typical amount

YOUR GENOTYPE

CHRNA3, rs1051730, AA

DESCRIPTION

Cigarette smoking is the single largest cause of preventable death and disease. Smoking harms nearly every organ of the body, causes many diseases, and shortens life on 7 - 8 years. Genetic background contributes about 50% to how much people smoke. For example, light smokers consume less than 10 cigarettes per day, while heavy smokers consume 20 or more. Certain genotypes are associated with smoking 1 cigarette per day more on average than the typical amount while other genotypes are associated with smoking 2 more per day on average.

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Smoking Cessation

YOUR RESULT

If you smoke, you have a typical likelihood of success of quitting

YOUR GENOTYPE

ANKK1, rs1800497, GG

DESCRIPTION

There are many benefits of stopping smoking. You will experience rapid normalization of blood pressure and heart rate, improvement in breathing and blood circulation. Over the long term, smoking cessation brings a much lower risk of developing many diseases as well as the chance to live longer years. Success of stopping smoking depends on the motivation to stop and the degree of dependence on cigarettes. It is estimated that genetic background contributes about 50% to the success of smoking cessation. Certain genotypes are associated with being more likely to successfully quit smoking, while other genotypes are associated with typical likelihood of success. Individuals who wish to quit smoking have various options for assistance including cognitive behavioral therapy, nicotine replacement patches and gum, as well as prescription medications.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

Appendix

This test was developed and performed by Human Longevity Clinical Laboratories. It has not been cleared or approved by the FDA. At this time, FDA approval is not required for clinical laboratory developed tests. The laboratory is regulated under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity testing. This test is used for clinical purposes and should not be regarded as investigational or for research.

1. Intended Use

The Health Nucleus Genomic Clinical Report is intended to be a screening test for apparently healthy individuals. The patient's health care provider will need to evaluate the patient's clinical status and will need to confirm the screening finding(s) which warrant a change in treatment via an appropriately licensed clinical laboratory's diagnostic test(s) before making such a change. These test results may have implications for family members. Genetic counseling is recommended for individuals who have questions or concerns about the genetic report.

1.1. Hereditary Disease Risk

This test is indicated for reporting genetic variants that are associated with high or medium genetic risk of developing hereditary (or monogenic) diseases. Findings of this test may warrant further evaluation. Such evaluations may include the use of appropriately validated diagnostic tests that are intended to diagnose the disease or condition related to a given genetic variant. If there are concerns regarding a particular genetic disease, or family history suggestive of a hereditary risk, a referral for a formal genetic consultation and discussion of appropriate diagnostic testing is recommended.

1.2. Pharmacogenomic Findings

This test is indicated for assessing how genetic variants may affect a person's response to prescribed medications. This test is not a substitute for clinical monitoring or other clinical evaluation. Only a health care provider should take action on the information contained in this test report. Do not stop taking or alter the dosage of any prescribed medications without consulting with your doctor beforehand.

1.3. Health Predisposition

This test is indicated for the reporting of combinations of genetic variants that are associated with genetic predisposition to common diseases. The variants included in the test are typically associated with a low genetic risk of developing a disease when considered independently, whereas the combined effects of multiple variants can contribute to increased risk of developing disease. The test results represent a percentile rank of the polygenic risk score as compared to research participants of European descent. The test is expected to provide less accurate results to people of non-European background.

The results of this test should not be used to guide medical care but rather to inform patient's lifestyle decisions. This test does not describe a person's overall risk of developing a disease, which is dependent on lifestyle and environmental factors in addition to genetic background. Even the highest reported genetic risk should not be interpreted as indicating the certainty of developing a disease, nor should the lowest risk be interpreted as immunity. This test is not intended to diagnose a disease or determine current state of health.

1.4. Nutritional and Wellness Traits

This test is indicated for reporting of common genetic variants that affect nutrition and wellness traits. Some variants contribute to nutrient deficiency and food sensitivity; others have an effect on behavior and fitness. This test does not describe a person's overall chance of developing a trait, which is

dependent on lifestyle and environmental factors in addition to genetic background. If two or more variants are associated with a trait, interpretation is provided for each variant separately.

The results of this test should not be used to guide medical care but rather to inform lifestyle decisions.

2. Sequencing Assay

Whole Genome Sequencing (WGS) on germline DNA was performed to ~30x mean depth using paired-end, 2 x 150 reads. Sequencing was performed using one of two techniques, dependent on the sample collection date.

Collected before January 1, 2019: Sequencing performed by Human Longevity Clinical Laboratories, 4570 Executive Dr, San Diego, CA 92121 (CAP#: 9013965; CLIA: 05D2094189).

Collected after January 1, 2019: Sequencing performed by HudsonAlpha Institute for Biotechnology Clinical Laboratory Services, 601 Genome Way, Huntsville, AL 35806 (CAP#: 8051488; CLIA: 01D2086581).

Alignment and variant calling were performed by Human Longevity Clinical Laboratories (CAP#: 9013965; CLIA: 05D2094189) on GRCh38/hg38 (GCA_000001405.15) using Isaac 01.14.02.06 and Starling2 2.5.26.13, respectively. Sequencing and bioinformatics pipelines were validated to assess three types of genetic alterations: single nucleotide variants (SNV), small insertions (<=7bp), and small deletions (<=7bp) within the high-confidence region (~93.25% of whole genome) defined by Human Longevity Clinical Laboratories based on the Illumina platinum genome for GRCh38/hg38 reference assembly.

The overall performance characteristics of the assay are as follows:
Sensitivity: SNV > 99%, Insertions > 92%, Deletions > 93%
Specificity: SNV > 99%, Insertions > 99%, Deletions > 99%

3. Analytics

3.1 Hereditary Disease Risk

Variants included in this report have met the ACMG guidelines criteria for classification as pathogenic and likely pathogenic. The variants include alterations interpreted by Human Longevity Clinical Laboratories (85% of variants) and ClinVar submitters (15% of variants) according to the ACMG guidelines [1, 2]. To be included, variant classification in ClinVar should be provided without contradictions by selected expert panels or by at least 2 of Human Longevity's trusted submitters, i.e. leading laboratories that have demonstrated adherence of their variant interpretation protocols to ACMG guidelines and consistent quality of variant classification.

Several variants in the test (APOE p.Cys130Arg (APOE e4 variant), BTD p.Asp444His, BTD p.Ala171Thr, HFE p.His63Asp, HOXB13 p.Gly84Glu, SERPINA1 p.Glu288Val) are included with a classification category risk factor. These variants have an incomplete penetrance and are associated with a lower risk of disease. The variants are included as they either modify the impact of other variants or are often included in similar tests. Relative and absolute risk of disease are provided for each such variant where clinical significance is well-established.

3.2. Pharmacogenomic Findings

Pharmacogenomic reporting is based on the guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) [3], the Dutch Pharmacogenetics Working Group (DPWG) [4], and recommendations provided in the FDA drug labels [5]. Any deviations reflect edits for brevity or clarity. The assay covers star alleles and variants in genes impacting efficacy, dosage, and adverse effects of specific drugs.

Pharmacogenomic reporting evaluates variants and their zygosity to determine a genotype comprised of two star alleles. In addition, phenotypes (e.g., Intermediate metabolizer) are predicted following CPIC guidelines. Star allele *1 signifies a normal (wild type) genotype and is characterized by the absence of any tested variants in the given gene. All other star alleles are defined as combinations of variants, with definitions available from CPIC star allele definition tables. In the case of an incomplete match of variants to star allele definitions, the star allele provided is based only on the variants completely shared with the definition. A result of "unable to determine" is displayed when the sequencing data for common variant(s) of the star alleles is not of sufficient quality or the genotypes are not unambiguously resolvable as a combination of two known star alleles. A common variant is defined as a variant with allele frequency of more than 1% in any 1000 Genomes subpopulation [6].

Allele specific copy number is only reported for CYP2D6 as part of the star allele diplotype, e.g., *1 x 2|*2 x 1 corresponds to 2 copies of allele *1 and 1 copy of *2. The impact of multiple copies of an allele is accounted for when reporting the phenotype as per CPIC guidelines.

3.3. Health Predisposition

This test utilizes polygenic risk scores, an innovative approach that combines the impact of many common variants of small effect into a single score. The common variants, typically associated with a low genetic risk of developing a disease when considered independently, have been shown to play a greater role in common diseases than rare monogenic variants [7 -9].

Polygenic risk models used in this test were defined based on findings of scientific studies called "Genome-Wide Association Studies" (termed GWAS). In these studies, scientists compare genomes of large groups of people, either with or without the disease, to find genetic variants that distinguish these two groups. The GWAS approach allows for the estimation of a variant-specific weight that is directly proportional to the strength of the association between the variant and the disease. A polygenic risk score is the sum of these weights for all variants that are shared between the polygenic risk model definition and the genome of the patient.

For each disease included in the test, available GWASs are reviewed to identify high-quality studies. Preference is given to studies that use a large number of genomes, are conducted by leading research groups, and that produce results corroborated by other studies. For each study selected, genetic variants associated with the disease and their weights are used as the basis of the polygenic risk model.

The percentile rank is the polygenic risk score of a patient as compared to that of Health Nucleus research participants of European background. For example, the 65th percentile means that the polygenic risk score is greater than 65% of the Health Nucleus research participants of European descent. The European background of research participants was determined based on the ancestry computed from the individuals' genomes and defined by the combined proportion of categories "Western European", "Eastern European" and "Southern European" being equal to or exceeding 60% from each included individual.

Please refer to https://www.humanlongevity.com/HN-Genomic-Clinical-White-Paper-Polygenic-1-0.pdf for more details on the development and validation of the polygenic risk models included in the test.

3.4. Nutritional and Wellness Traits

This test includes a set of models, each of which comprises one or two common genetic variants contributing to development of a given trait. The genetic variants used in models and interpretation of their effects are identified by a comprehensive review of scientific literature for a specific trait. When selecting studies for inclusion, preference is given to ones that used a large number of people to study the trait, were conducted by leading research groups, and produced results that are corroborated by other studies. The research into genetics of some traits is ongoing. The level of current scientific evidence is ranked using a four-tier system - "preliminary" (one star), "moderate" (two stars), "strong" (three stars), "established" (four stars) – presented next to each trait.

Results interpretation is provided for each variant separately. For example, "GDF5, rs143383 GA". GDF5 is a name of the gene in which the variant occurs; rs143383 points to the location of the specific DNA base pair in the genome. GA indicates the DNA basepair (or "genotype") at this location: there is guanine (G) in one copy of the GDF5 gene and adenine (A) in another copy. An interpretation of the result, for example, "You are likely at increased risk of Achilles tendon injury or inflammation", is provided next to the genotype.

PATIENT INFORMATION

PATIENT NAME:
Patient, Sample

PATIENT ID:	SEX:	DOB:
MRN-1234	Male	02/14/1959

4. Reporting Scope

4.1 Hereditary Disease Risk

The variant list included in this test encompasses 91,087 variants covering 1,498 genes and 1,624 diseases. Please refer to the table below for the number of genes and variants related to specific disease categories.

For a full list of genes, please refer to https://www.humanlongevity.com/HN-Genomic-Clinical-Gene-List-5-0.pdf.

HEALTH CATEGORY	TOTAL GENES ASSESSED	TOTAL VARIANTS ASSESSED
Cardiovascular Disorder	55	5226
Dental Disorder	6	74
Endocrine Disorder	56	1957
Gastrointestinal Disorder	7	139
Hearing Disorder	32	1433
Hematologic Disorder	53	4018
Hereditary Cancer	87	22530
Immunological Disorder	72	2187
Kidney Disorder	39	2999

HEALTH CATEGORY	TOTAL GENES ASSESSED	TOTAL VARIANTS ASSESSED
Liver Disorder	10	422
Metabolic Disorder	171	6263
Musculoskeletal Disorder	104	7258
Neurodegenerative Disorder	28	555
Neurologic Disorder	277	11619
Respiratory Disorder	27	1493
Skin Disorder	46	1675
Syndromic Disorder	341	17012
Vision Disorder	91	4227

4.2. Pharmacogenomic Findings

For the list of genes and variants detected by this test, please refer to https://www.humanlongevity.com/HN-Genomic-Clinical-Gene-List-5-0.pdf. A star allele *1 (normal or wild type genotype) signifies the absence of the targeted alleles and does not indicate the absence of other variants not covered by the assay.

4.3. Health Predisposition

For the list of variants included in each polygenic risk model, variants' weights characterizing the impact of each variant, as well as scientific studies, from which the variants were extracted, please refer to https://www.humanlongevity.com/HN-Genomic-Clinical-Gene-List-5-0.pdf.

There is a small overlap between variants included in the polygenic risk models and the scope of the "Hereditary Disease Risk" test. Specifically, the APOE e4 variant is included in the Alzheimer's disease polygenic risk model and the c.*97G>A variant in the F2 gene and the factor V Leiden variant in the F5 gene are included in the venous thromboembolism polygenic risk model. The polygenic risk scores for these diseases are expected to be higher when corresponding variants are identified by the "Hereditary Disease Risk" test.

4.4. Nutritional and Wellness Traits

For the list of variants included in trait models, please refer to https://www.humanlongevity.com/HN-Genomic-Clinical-Gene-List-5-0.pdf.

5. Limitations

5.1 Hereditary Disease Risk

This test is validated to generate a high-quality consensus whole genome sequence, however, the following limitations need to be considered:

- Only variants included in the pre-defined list of variants described in section 4.1 are reported when identified. Other potentially pathogenic rare variants in the panel's genes as well as novel variants may be present in the patient's DNA and are not reported. A negative test result, therefore, does not completely rule out the possibility that the patient has other variants that could affect his or her health and does not rule out the possibility that the patient is a carrier.
- The "Hereditary Disease Risk" test excludes common variants included in the polygenic risk scores in the "Health Predisposition" assessment (with the exception of the three variants listed in the section 4.3). Thus, apart from the Alzheimer's disease and the venous thromboembolism polygenic risk models, the results of the two tests are independent and a patient can be negative for one but positive for another assessment.
- The technology currently available for whole genome sequencing does not address the entire human genome: this assay assesses 90% - 93% of the human genome representing the high-confidence regions. The regions of the genome not reported in this test include regions where the human reference genome has not been completely resolved or where duplications of genetic regions impair accurate alignment. The presence of alterations outside the evaluated regions in the genome is not identified and therefore cannot be ruled out.
- Only single nucleotide variants, small insertions (<=7bp), and deletions (<=7bp) within the high-confidence regions are reported in this test.
- Variants included in the reporting scope but not meeting sufficient sequencing coverage in a given sample are not reported.

5.2 Pharmacogenomic Findings

This test is validated to generate accurate star allele calls and associated phenotypes, however, the following limitations need to be considered:

- Other genetic and non-genetic factors such as drug-drug interactions are not considered in this test but may also impact drug response.
- This test does not cover HLA genes, although some of them are linked to significant adverse effects to certain drugs, including carbamazepine and abacavir.
- Not all variants relevant to known star alleles and not all known star alleles are included in this test due to the absence of functional characterization in the CPIC guidelines or star allele definition tables.
- In some instances, CPIC guidelines provide variants comprising a star allele but do not provide a phenotype (e.g., SLCO1B1 *14). In these cases, only a genotype is reported.
- The methodology used in this test is unable to determine the allelic phase. In certain instances, this leads to ambiguity in genotype calling (e.g., SLCO1B1 *1|*15 cannot be resolved from SLCO1B1 *1B|*5), leading to either an "unable to determine" output in cases where phenotypes are different, or output of two or more diplotypes in cases where all diplotypes are associated with the same phenotype.
- For X-linked haplotypes (G6PD gene) in males, the given diplotype consisting of two identical variants should be interpreted as a single variant.

5.3 Health Predisposition

This test is validated to generate accurate polygenic risk score calculations, however, the following caveats need to be considered:

- The polygenic risk models included in this report only describe the contribution of the genetic background. Other important contributors to disease risk are lifestyle and environmental factors that are not taken into account by the results provided in this report.
- This test provides genetic risk information based on assessment of specific genetic variants described in section 4.3. It does not report on the entire genetic profile and excludes rare variants included in scope of the "Hereditary Disease Risk" test (with the exception of the three variants listed in the section 4.3). Thus, apart from the Alzheimer's disease and the venous thromboembolism polygenic risk models, the results of the two tests are independed and a patient can be negative for one but positive for another assessment
- This test does not detect all common variants related to a given disease. The absence of variants tested does not rule out the presence of other genetic variants that may be related to the disease. There are several reasons for some genetic variants to be excluded from this test:
    - This test reports on the genetic variants reported in published scientific studies at a single point in time and is considered current as of the report date. The list of articles that were consulted in preparing the report is not necessarily a comprehensive list, and other studies may exist that are relevant to the test results. New associations are discovered daily, some of which may relate to genes and variants that are included in this report or represent newly discovered genes and variants. A health care professional should reassess the results provided in this report as future relevant evidence becomes available
    - Only genetic variants meeting the validated parameters are included in this test, please review the sequencing limitation details provided in the section 1.5.
- Polygenic risk models used in this test were originally developed using genomes of people of European descent and may provide less accurate results to people of other ethnicities.

5.4. Nutritional and Wellness Traits

This test is validated to generate accurate genotype results, however, the following caveats need to be considered:

- The trait models included in this report only describe the contribution of the genetic background. Other important contributors to trait development are lifestyle and environmental factors that are not taken into account by the results provided in this report.
- This test does not detect all common variants related to a given trait. See item 5.3 for additional details as polygenic risk models have a similar limitation.
- Models originally developed using genomes of a specific ethnicity cannot always be successfully used to predict physical traits for people of a different ethnicity. We recommend consulting https://www.humanlongevity.com/your-results-guide-5-0.pdf to learn for whom the models provide the most accurate result.
- The patient may get a different result using a test from a different company even if the test is for the same trait. Other companies offering genetic tests may be detecting different genetic variants for the traits. They could be using different sequencing technology or include evidence from different scientific studies.

6. References

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Laboratory Director: Henry Tsai, MD, PhD