Blueprint Genetics

Hypertrophic Cardiomyopathy (HCM) Panel

Test code: CA1901

Is a 92 gene panel that includes assessment of non-coding variants.

In addition, it also includes the maternally inherited mitochondrial genome.
Is ideal for patients who fulfill clinical diagnostic criteria for hypertrophic cardiomyopathy (HCM) or have significant LVH without a history of high blood pressure or aortic stenosis .

About Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is one of the most common human monogenic disorders with prevalence estimates of 1:500, predicting approximately 600,000 persons with HCM in the US alone. It is also the most common cause for sudden cardiac death among young adults. HCM is generally defined by the development of unexplained left ventricular hypertrophy (LVH) and commonly caused by mutations in cardiac sarcomere genes. In HCM, LVH occurs in a non-dilated ventricle in the absence of other cardiac or systemic disease capable of producing the observed abnormal LV wall thickness. Systemic diseases that can mimic HCM are for example pressure overload due to long-standing hypertension or aortic stenosis, or storage/infiltrative disorders (Fabry disease, Pompe disease) or certain syndromes (Noonan spectrum diseases, Danon disease). The clinical manifestations of HCM range from asymptomatic LVH to progressive heart failure to ventricular arrhythmias and sudden cardiac death (SCD). Atrial fibrillation and atrioventricular conduction abnormalities can also manifest. HCM is the most common cause of sudden cardiac death under age of 30 and also the most common cause for SCD in athletes. SCD can be the first clinical manifestation even in patients with no clear LVH. Symptoms can vary from individual to individual even within the same family. Common symptoms include shortness of breath (particularly during exercise), chest pain, palpitations, orthostasis, presyncope, and syncope. Most often the LVH of HCM becomes apparent during adolescence or young adulthood, although it may also develop later in life, in infancy, or in childhood.

Availability

4 weeks

Gene Set Description

Genes in the Hypertrophic Cardiomyopathy (HCM) Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCC9	Atrial fibrillation, Cantu syndrome, Dilated cardiomyopathy (DCM)	AD	27	46
ACAD9	Acyl-CoA dehydrogenase family, deficiency	AR	26	61
ACADVL	Acyl-CoA dehydrogenase, very long chain, deficiency	AR	119	282
ACTA1	Myopathy	AD/AR	68	212
ACTC1	Left ventricular noncompaction, Hypertrophic cardiomyopathy (HCM), Cardiomyopathy, restrictive, Atrial septal defect, Dilated cardiomyopathy (DCM)	AD	23	63
ACTN2	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	11	44
AGK*	Sengers syndrome, Cataract 38	AR	18	27
AGL	Glycogen storage disease	AR	142	245
ALPK3	Pediatric cardiomyopathy	AR	12	6

APOA1	Amyloidosis, systemic nonneuronopathic, Hypoalphalipoproteinemia	AD/AR	28	71
BAG3	Dilated cardiomyopathy (DCM), Myopathy, myofibrillar	AD	39	62
BRAF*	LEOPARD syndrome, Noonan syndrome, Cardiofaciocutaneous syndrome	AD	134	65
CACNA1C*	Brugada syndrome, Timothy syndrome, Neurodevelopmental disorder	AD	19	68
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	AD	24	43
COX15	Leigh syndrome, Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency	AR	7	5
CPT2	Carnitine palmitoyltransferase II deficiency	AR	72	111
CSRP3	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	4	30
DES	Dilated cardiomyopathy (DCM), Myopathy, myofibrillar, Scapuloperoneal syndrome, neurogenic, Kaeser type	AD/AR	64	124
ELAC2	Combined oxidative phosphorylation deficiency 17	AR	11	15
EPG5	Vici syndrome	AR	36	66
FBXL4	Mitochondrial DNA depletion syndrome	AR	55	47
FHL1*	Myopathy with postural muscle atrophy, Emery-Dreifuss muscular dystrophy, Reducing bod myopathy	XL	26	62
FHOD3	Cardiomyopathy, familial hypertrophic	AD		1
FLNC*	Myopathy	AD	54	109
FXN*	Friedreich ataxia	AR	13	63
GAA	Glycogen storage disease	AR	193	573
GLA	Fabry disease	XL	226	937
GSK3B	Hypertrophic cardiomyopathy, Dilated cardiomyopathy (DCM)		2	
HRAS	Costello syndrome, Congenital myopathy with excess of muscle spindles	AD	43	31
JPH2	Hypertrophic cardiomyopathy (HCM)	AD	3	13
KLHL24	Epidermolysis bullosa simplex, generalized, with scarring and hair loss, Dilated cardiomyopathy (DCM), Hypertrophic cardiomyopathy (HCM)	AD/AR	5	5
KRAS*	Noonan syndrome, Cardiofaciocutaneous syndrome	AD	63	35
LAMP2	Danon disease	XL	62	101
MAP2K1	Cardiofaciocutaneous syndrome	AD	45	23
MAP2K2	Cardiofaciocutaneous syndrome	AD	21	35
MIPEP	Combined oxidative phosphorylation deficiency 31	AR	5	8

MT-ATP6	Neuropathy, ataxia, and retinitis pigmentosa, Leber hereditary optic neuropathy, Ataxia and polyneuropathy, adult-onset, Cardiomyopathy, infantile hypertrophic, Leigh syndrome, Striatonigral degeneration, infantile, mitochondrial	Mitochondrial	19
MT-ATP8	Cardiomyopathy, apical hypertrophic, and neuropathy, Cardiomyopathy, infantile hypertrophic	Mitochondrial	4
MT-CO1	Myoglobinuria, recurrent, Leber hereditary optic neuropathy, Sideroblastic anemia, Cytochrome C oxidase deficiency, Deafness, mitochondrial	Mitochondrial	17
MT-CO2	Cytochrome c oxidase deficiency	Mitochondrial	8
MT-CO3	Cytochrome c oxidase deficiency, Leber hereditary optic neuropathy	Mitochondrial	9
MT-CYB		Mitochondrial	69
MT-ND1	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia	Mitochondrial	21
MT-ND2	Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	6
MT-ND3	Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	7
MT-ND4	Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	11
MT-ND4L	Leber hereditary optic neuropathy	Mitochondrial	2
MT-ND5	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	19
MT-ND6	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Oncocytoma, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	16
MT-RNR1	Deafness, mitochondrial	Mitochondrial	3
MT-RNR2	Chloramphenicol toxicity/resistance	Mitochondrial	2
MT-TA		Mitochondrial	4
MT-TC	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3
MT-TD		Mitochondrial	1
MT-TE	Diabetes-deafness syndrome, Mitochondrial myopathy, infantile, transient, Mitochondrial myopathy with diabetes	Mitochondrial	5
MT-TF	Myoclonic epilepsy with ragged red fibers, Nephropathy, tubulointerstitial, Encephalopathy, mitochondrial, Epilepsy, mitochondrial, Myopathy, mitochondrial, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	7
MT-TG		Mitochondrial	3
MT-TH		Mitochondrial	4

MT-TI		Mitochondrial	7	
MT-TK	Myoclonic epilepsy with ragged red fibers, Leigh syndrome	Mitochondrial	5	
MT-TL1	Cytochrome c oxidase deficiency, Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Diabetes-deafness syndrome, Cyclic vomiting syndrome, SIDS, susceptibility to	Mitochondrial	14	
MT-TL2	Mitochondrial multisystemic disorder, Progressive external ophthalmoplegia, Mitochondrial Myopathy, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	5	
MT-TM	Leigh syndrome, Mitochondrial multisystemic disorder	Mitochondrial	1	
MT-TN	Progressive external ophthalmoplegia, Mitochondrial multisystemic disorder	Mitochondrial	3	
MT-TP		Mitochondrial	2	
MT-TQ	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TR	Encephalopathy, mitochondrial	Mitochondrial	2	
MT-TS1	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	10	
MT-TS2	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TT		Mitochondrial	5	
MT-TV	Hypertrophic cardiomyopathy (HCM), Leigh syndrome, Mitochondrial multisystemic disorder, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	3	
MT-TW	Leigh syndrome, Myopathy, mitochondrial	Mitochondrial	8	
MT-TY	Mitochondrial multisystemic disorder	Mitochondrial	4	
MTO1	Combined oxidative phosphorylation deficiency	AR	16	24
MYBPC3	Left ventricular noncompaction, Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	482	1048
MYH7	Hypertrophic cardiomyopathy (HCM), Myopathy, myosin storage, Myopathy, distal, Dilated cardiomyopathy (DCM)	AD	305	986
MYL2	Hypertrophic cardiomyopathy (HCM), Infantile type I muscle fibre disease and cardiomyopathy	AD	21	67
MYL3	Hypertrophic cardiomyopathy (HCM)	AD/AR	12	41
NDUFAF2	Mitochondrial complex I deficiency, Leigh syndrome	AR	9	8
PLN	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD/AR	8	30
PRKAG2#	Hypertrophic cardiomyopathy (HCM), Wolff-Parkinson-White syndrome, Glycogen storage disease of heart, lethal congenital	AD	19	57
PTPN11	Noonan syndrome, Metachondromatosis	AD	135	140

RAF1	LEOPARD syndrome, Noonan syndrome, Dilated cardiomyopathy (DCM)	AD	45	53
RIT1	Noonan syndrome	AD	23	26
SLC25A4	Progressive external ophthalmoplegia with mitochondrial DNA deletions, Mitochondrial DNA depletion syndrome	AD/AR	12	14
SOS1	Noonan syndrome	AD	44	71
TNNC1	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	9	24
TNNI3	Hypertrophic cardiomyopathy (HCM), Cardiomyopathy, restrictive, Dilated cardiomyopathy (DCM)	AD/AR	56	129
TNNT2	Left ventricular noncompaction, Hypertrophic cardiomyopathy (HCM), Cardiomyopathy, restrictive, Dilated cardiomyopathy (DCM)	AD	61	148
TPM1	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	34	98
TTR	Dystransthyretinemic hyperthyroxinemia, Amyloidosis, hereditary, transthyretin-related	AD	52	148
VCL	Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD	8	30

*Some regions of the gene are duplicated in the genome. Read more.

The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#). Due to possible limitations these genes may not be available as single gene tests.

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
ACADVL	Chr17:7123160	c.-144_-132delCCCAGCATGCCCCinsT	NM_000018.3	
ACADVL	Chr17:7125469	c.822-27C>T	NM_001270447.1	rs374911841
ACADVL	Chr17:7125485	c.822-11T>G	NM_001270447.1	
ACADVL	Chr17:7126199	c.1146+15C>T	NM_001270447.1	rs202237278
ACADVL	Chr17:7126948	c.1252-15A>G	NM_001270447.1	rs765390290
ACADVL	Chr17:7127894	c.1747+23C>T	NM_001270447.1	rs147546456
ACTC1	Chr15:35080829	c.*1784T>C	NM_005159.4	

AGL	Chr1:100381954	c.4260-12A>G	NM_000028.2	rs369973784
APOA1	Chr11:116708299	c.-21+22G>A	NM_000039.1	
APOA1	Chr11:116708365	c.-65A>C	NM_000039.1	
GAA	Chr17:78078341	c.-32-13T>G	NM_000152.3	rs386834236
GAA	Chr17:78078341	c.-32-13T>A	NM_000152.3	
GAA	Chr17:78078351	c.-32-3C>A/G	NM_000152.3	
GAA	Chr17:78078352	c.-32-2A>G	NM_000152.3	
GAA	Chr17:78078353	c.-32-1G>C	NM_000152.3	
GAA	Chr17:78078369	c.-17C>T	NM_000152.3	
GAA	Chr17:78082266	c.1076-22T>G	NM_000152.3	rs762260678
GAA	Chr17:78090422	c.2190-345A>G	NM_000152.3	
GAA	Chr17:78092432	c.2647-20T>G	NM_000152.3	
GLA	ChrX:100653945	c.640-11T>A	NM_000169.2	
GLA	ChrX:100654735	c.640-801G>A	NM_000169.2	rs199473684
GLA	ChrX:100654793	c.640-859C>T	NM_000169.2	rs869312374
GLA	ChrX:100656225	c.547+395G>C	NM_000169.2	
MYBPC3	Chr11:47353394	c.*26+2T>C	NM_000256.3	
MYBPC3	Chr11:47353821	c.3628-12C>G	NM_000256.3	rs371428751
MYBPC3	Chr11:47359371	c.2309-26A>G	NM_000256.3	
MYBPC3	Chr11:47360310	c.2149-80G>A	NM_000256.3	
MYBPC3	Chr11:47364709	c.1227-13G>A	NM_000256.3	rs397515893
MYBPC3	Chr11:47364832	c.1224-19G>A	NM_000256.3	rs587776699
MYBPC3	Chr11:47364865	c.1224-52G>A	NM_000256.3	rs786204336
MYBPC3	Chr11:47365750	c.1091-575A>C	NM_000256.3	
MYBPC3	Chr11:47367305	c.1090+453C>T	NM_000256.3	
MYBPC3	Chr11:47368602	c.906-22G>A	NM_000256.3	rs756267771
MYBPC3	Chr11:47368616	c.906-36G>A	NM_000256.3	rs864622197
PLN	Chr6:118869382	c.-271A>G	NM_002667.4	
PLN	Chr6:118869417	c.-236C>G	NM_002667.4	rs188578681
PTPN11	Chr12:112915602	c.934-59T>A	NM_002834.3	
TPM1	Chr15:63349172	c.241-12_241-11delCTinsTG	NM_001018005.1	rs199476309

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *MTO1* (NM_133645:7;NM_001123226:8). Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not d etect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test Performance

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

The performance metrics listed below are from an initial validation performed at our main laboratory in Finland. The performance metrics of our laboratory in Seattle, WA, are equivalent.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	99.2% (7,745/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
Size range (0.1-47 Mb)	100% (25/25)	

The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics

Mean sequencing depth	143X
Nucleotides with >20x sequencing coverage (%)	99.86%

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	Specificity %
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	99,997%
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%

Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent diagnostics where customers have easy access to crucial details of the analysis process.

Clinical Interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the ACMG guideline 2015.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic

using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation variant databases used to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

Reference information

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Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015 Mar 5, in press.

CPT code(s) *

81439, 81460, 81465

* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

ICD Codes

Refer to the most current version of ICD-10-CM manual for a complete list of ICD-10 codes.

Sample Requirements

- Blood (min. 1ml) in an EDTA tube
- Extracted DNA, min. 2 µg in TE buffer or equivalent
- Saliva (Please see Sample Requirements for accepted saliva kits)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

We do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue. In addition, if the patient is affected with a hematological malignancy, DNA extracted from a non-hematological source (e.g. skin fibroblasts) is strongly recommended.

Please note that, in rare cases, mitochondrial genome (mtDNA) variants may not be detectable in blood or saliva in which case DNA extracted from post-mitotic tissue such as skeletal muscle may be a better option.

Read more about our sample requirements here.

For Patients

Other

- Al-Khatib SM et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Circulation. 2017 Oct 30 [Epub ahead of print].
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- Hypertrophic Cardiomyopathy Association
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- NORD - Pediatric Cardiomyopathy