Blueprint Genetics

Cataract Panel

Test code: OP0201

Is a 113 gene panel that includes assessment of non-coding variants.

In addition, it also includes the maternally inherited mitochondrial genome.
Is ideal for patients with a clinical suspicion / diagnosis of congenital cataracts or a syndrome with cataracts as a feature.

About Cataract

Cataract is defined as opacification of the normally transparent crystalline lens. Cataract can be classified as congenital, infantile, juvenile, presenile, and senile. Congenital cataract (CC) is present at birth or during early childhood and is one of the most common ocular diseases causing visual impairment or blindness in children worldwide. Nuclear cataract is the most common type of hereditary CC and is characterized by the opacification limited to the embryonic and/or fetal nuclei of the lens (PMID: 24384146). It can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner, of which the autosomal dominant mode is the most common. Nuclear CC is genetically highly heterogeneous. Mutations in lens crystallins (*CRYAA*, *CRYAB*, *CRYBB1*, *CRYBB2*, *CRYBB3*, *CRYGC*, *CRYGD*) explain approximately half of the cases, followed by connexins (*GJA3*, *GJA8*). Congenital nuclear cataract can be isolated (70%) or associated with other ocular disorders, such as microphthalmia or aniridia. It may also be part of multisystem genetic disorders such as Nance-Horan syndrome (*NHS*), Lowe syndrome (*OCRL*) or neurofibromatosis type 2 (*NF2*). The prevalence of cataract in children has been estimated between 1-15:10,000.

Availability

4 weeks

Gene Set Description

Genes in the Cataract Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCB6	Blood group, Langereis system, Pseudohyperkalemia, Dyschromatosis universalis hereditaria, Microphthalmia, isolated, with coloboma 7	AD/BG	9	20
ADAMTS18	Knobloch syndrome 2, Microcornea, myopic chorioretinal atrophy, and telecanthus, Retinal dystrophy, early onset, autosomal recessive	AR	4	14
ADAMTSL4	Ectopia lentis, isolated	AR	11	27
AGK*	Sengers syndrome, Cataract 38	AR	18	27
ALDH18A1	Spastic paraplegia, Cutis laxa	AD/AR	22	30
BCOR	Microphthalmia, syndromic, Oculofaciocardiodental syndrome	XL	40	53
BFSP1	Cataract 33	AR	4	7
BFSP2	Cataract	AD	2	7
CHMP4B	Cataract 31, multiple types	AD	2	2
COL11A1	Marshall syndrome, Fibrochondrogenesis, Stickler syndrome type 2	AD/AR	34	94
COL18A1	Knobloch syndrome	AR	27	31

COL2A1	Avascular necrosis of femoral head, Rhegmatogenous retinal detachment, Epiphyseal dysplasia, with myopia and deafness, Czech dysplasia, Achondrogenesis type 2, Platyspondylic dysplasia Torrance type, Hypochondrogenesis, Spondyloepiphyseal dysplasia congenital (SEDC), Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type, Kniest dysplasia, Spondyloperipheral dysplasia, Mild SED with premature onset arthrosis, SED with metatarsal shortening, Stickler syndrome type 1	AD	180	561
COL4A1	Schizencephaly, Anterior segment dysgenesis with cerebral involvement, Retinal artery tortuosity, Porencephaly, Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps, Brain small vessel disease	AD	58	107
CRYAA	Cataract	AD/AR	12	24
CRYAB	Cataract, myofibrillar myopathy and cardiomyopathy, Congenital cataract and cardiomyopathy, Dilated cardiomyopathy (DCM), Myopathy, myofibrillar, Cataract 16, multiple types, Myopathy, myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related	AD	14	28
CRYBA1	Cataract 10, multiple types	AD	9	13
CRYBA4	Cataract 23	AD	4	10
CRYBB1	Cataract	AD/AR	7	18
CRYBB2*	Cataract	AD	10	27
CRYBB3	Cataract	AR	3	7
CRYGC	Cataract	AD	10	28
CRYGD	Cataract	AD	10	26
CRYGS	Cataract, progressive polymorphic cortical	AD	3	8
CTDP1	Congenital cataracts, facial dysmorphism, and neuropathy	AR	1	1
CYP27A1	Cerebrotendinous xanthomatosis	AR	69	110
DNMBP	Cataract	AR		
EPHA2	Cataract 6, multiple types	AD/AR	7	20
ERCC2	Xeroderma pigmentosum, Trichothiodystrophy, photosensitive, Cerebrooculofacioskeletal syndrome 2	AR	26	98
ERCC5	Xeroderma pigmentosum, Xeroderma pigmentosum/Cockayne syndrome	AR	21	54
ERCC6*	Xeroderma Pigmentosum-Cockayne Syndrome, De Sanctis-Cacchione syndrome	AD/AR	87	135
ERCC8	UV-sensitive syndrome, Cockayne syndrome	AR	34	64
EYA1	Otofaciocervical syndrome, Branchiootic syndrome, Branchiootorenal syndrome	AD	56	218
FAM126A	Leukodystrophy, hypomyelinating	AR	8	12

FOXE3	Aphakia, congenital primary, Anterior segment mesenchymal dysgenesis, Cataract 34, Aortic aneurysm, familial thoracic	AR/AD	9	29
FTL	Hyperferritinemia-cataract syndrome, L-ferritin deficiency, Neurodegeneration with brain iron accumulation	AD/AR	21	63
FYCO1	Cataract	AR	10	20
FZD4	Retinopathy of prematurity, Exudative vitreoretinopathy	AD/Digenic	14	90
GALE	Galactose epimerase deficiency	AR	12	26
GALK1	Galactokinase deficiency	AR	15	44
GALT	Galactosemia	AR	238	330
GCNT2	Blood group, Ii, Adult i pheno without cataract, Cataract 13 with adult i pheno	BG/AR	11	11
GJA1*	Oculodentodigital dysplasia mild type, Oculodentodigital dysplasia severe type, Syndactyly type 3	AD/AR	31	107
GJA3	Cataract	AD	14	43
GJA8	Cataract	AD/AR	20	61
HSF4	Cataract	AD/AR	8	18
LEMD2	Cataract 46, juvenile onset, Arrhythmogenic right ventricular cardiomyopathy (ARVC), Dilated cardiomyopathy (DCM)	AR	1	1
LIM2	Cataract	AD/AR	2	4
MAF	Ayme-Gripp syndrome, Cataract 21, multiple types	AD	21	22
MIP	Cataract 15, multiple types	AD	11	27
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	
MYH9	Sebastian syndrome, May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, Macrothrombocytopenia and progressive sensorineural deafness, Deafness, autosomal dominant 17	AD	25	117
NDP	Exudative vitreoretinopathy, Norrie disease	XL	31	167
NF2	Schwannomatosis, Neurofibromatosis	AD	66	433
NHS	Nance-Horan syndrome, Cataract	XL	36	52
OCRL	Lowe syndrome, Dent disease	XL	47	264
OPA3	Optic atrophy, 3-methylglutaconic aciduria	AD/AR	13	15
P3H2	Myopia, high, with cataract and vitreoretinal degeneration	AR	7	7
PAX6	Aniridia, cerebellar ataxia, and mental retardation (Gillespie syndrome), Keratitis, Coloboma, ocular, Cataract with late-onset corneal dystrophy, Morning glory disc anomaly, Foveal hypoplasia, Aniridia, Optic nerve hypoplasia, Peters anomaly	AD	144	550
PITX3	Cataract, Anterior segment mesenchymal dysgenesis	AD	5	11
PXDN	Anterior segment dysgenesis 7	AR	7	14
RAB18#	Warburg micro syndrome 3	AR	5	5
RAB3GAP1	Warburg micro syndrome	AR	29	66
RAB3GAP2#	Warburg micro syndrome, Martsolf syndrome	AR	11	15
RECQL4	Baller-Gerold syndrome, RAPADILINO syndrome, Rothmund-Thomson syndrome	AR	82	114
SIL1	Marinesco-Sjogren syndrome	AR	14	49
SIPA1L3	Cataract 45	AR	2	4
SLC16A12	Cataract 47	AD	3	18
SLC33A1*	Congenital cataracts, hearing loss, and neurodegeneration, Spastic paraplegia 42, autosomal dominant	AD/AR	6	7
TBC1D20	Warburg micro syndrome 4	AR	6	6
TDRD7	Cataract	AR	5	5

TFAP2A	Branchiooculofacial sydrome	AD	23	42
TMEM70	Mitochondrial complex V (ATP synthase) deficiency	AR	12	18
VIM	Cataract 30, multiple types	AD	2	3
VSX2	Microphthalmia, isolated 2, Microphthalmia, isolated, with coloboma 3	AR	9	13
WFS1	Wolfram syndrome, Wolfram-like syndrome, autosomal dominant, Deafness, autosomal dominant 6/14/38, Cataract 41	AD/AR	69	362
WRN*	Werner syndrome	AR	64	107
XYLT2	Spondyloocular syndrome	AR	2	10

*

Some, or all, of the gene is duplicated in the genome. Read more.

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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
COL11A1	Chr1:103386637	c.3744+437T>G	NM_080629.2	
COL11A1	Chr1:103488576	c.1027-24A>G	NM_080629.2	
COL11A1	Chr1:103491958	c.781-450T>G	NM_080629.2	rs587782990
COL2A1	Chr12:48379984	c.1527+135G>A	NM_001844.4	
COL4A1	Chr13:110802675	c.*35C>A	NM_001845.4	
COL4A1	Chr13:110802678	c.*32G>A/T	NM_001845.4	

COL4A1	Chr13:110802679	c.*31G>T	NM_001845.4	
ERCC5	Chr13:103514354	c.881-26T>G	NM_000123.3	
ERCC6	Chr10:50681659	c.2599-26A>G	NM_000124.3	rs4253196
ERCC8	Chr5:60223572	c.173+1119G>C	NM_000082.3	
ERCC8	Chr5:60223645	c.173+1046A>G	NM_000082.3	
EYA1	Chr8:72156939	c.1051-12T>G	NM_000503.4	
EYA1	Chr8:72211483	c.640-15G>A	NM_000503.4	
FTL	Chr19:49468350	c.-415C>A	NM_000146.3	
FTL	Chr19:49468574	c.-189_-161delGGTCCCGCGGGTCTGTCTCTTGCTTCAAC	NM_000146.3	
FTL	Chr19:49468575	c.-190C>T	NM_000146.3	
FTL	Chr19:49468579	c.-186C>G	NM_000146.3	
FTL	Chr19:49468581	c.-184C>T	NM_000146.3	
FTL	Chr19:49468583	c.-182C>T	NM_000146.3	
FTL	Chr19:49468583	c.-182_-178delCGGGTinsTGGGG	NM_000146.3	
FTL	Chr19:49468586	c.-175_-170delGTCTCT	NM_000146.3	rs398124639
FTL	Chr19:49468587	c.-178T>G	NM_000146.3	
FTL	Chr19:49468589	c.-176T>C	NM_000146.3	
FTL	Chr19:49468593	c.-168_-165delGCTT	NM_000146.3	
FTL	Chr19:49468594	c.-171C>G	NM_000146.3	
FTL	Chr19:49468597	c.-168G>A/C/T	NM_000146.3	rs398124635
FTL	Chr19:49468597	c.-168G>T	NM_000146.3	
FTL	Chr19:49468597	c.-168G>C	NM_000146.3	
FTL	Chr19:49468597	c.-168G>A	NM_000146.3	
FTL	Chr19:49468598	c.-167C>A/T	NM_000146.3	
FTL	Chr19:49468598	c.-167C>A	NM_000146.3	
FTL	Chr19:49468598	c.-167C>T	NM_000146.3	
FTL	Chr19:49468599	c.-166T>C	NM_000146.3	
FTL	Chr19:49468601	c.-164C>A/T	NM_000146.3	rs398124637
FTL	Chr19:49468601	c.-164C>G	NM_000146.3	
FTL	Chr19:49468601	c.-158_-143delTGTTTGGACGGAACAG	NM_000146.3	
FTL	Chr19:49468602	c.-163A>C/G/T	NM_000146.3	

FTL	Chr19:49468602	c.-163A>T	NM_000146.3	
FTL	Chr19:49468602	c.-163A>G	NM_000146.3	
FTL	Chr19:49468602	c.-163A>C	NM_000146.3	
FTL	Chr19:49468602	c.-161_-160delCA	NM_000146.3	
FTL	Chr19:49468603	c.-161delC	NM_000146.3	
FTL	Chr19:49468604	c.-161C>T	NM_000146.3	rs398124636
FTL	Chr19:49468604	c.-161C>A/G	NM_000146.3	
FTL	Chr19:49468605	c.-160A>G	NM_000146.3	rs398124633
FTL	Chr19:49468606	c.-159G>C	NM_000146.3	rs398124634
FTL	Chr19:49468608	c.-157G>A	NM_000146.3	
FTL	Chr19:49468611	c.-154T>G	NM_000146.3	
FTL	Chr19:49468612	c.-153G>A	NM_000146.3	
FTL	Chr19:49468612	c.-153_-152delGGinsCT	NM_000146.3	
FTL	Chr19:49468614	c.-151A>C	NM_000146.3	
FTL	Chr19:49468614	c.-151A>G	NM_000146.3	
FTL	Chr19:49468615	c.-150C>A	NM_000146.3	
FTL	Chr19:49468616	c.-149G>C	NM_000146.3	rs398124638
FTL	Chr19:49468617	c.-148G>C	NM_000146.3	
FTL	Chr19:49468621	c.-144A>T	NM_000146.3	
FTL	Chr19:49468655	c.-110C>T	NM_000146.3	
FTL	Chr19:49468720	c.-44delT	NM_000146.3	rs772029022
GALK1	Chr17:73761239	c.-22T>C	NM_000154.1	rs545362817
GALT	Chr9:34646606	c.-96T>G	NM_000155.3	
GALT	Chr9:34647075	c.83-11T>G	NM_000155.3	
GALT	Chr9:34648082	c.508-29delT	NM_000155.3	rs111033711
GALT	Chr9:34648519	c.687+66T>A	NM_000155.3	
GALT	Chr9:34648904	c.820+13A>G	NM_000155.3	rs111033768
GALT	Chr9:34649617	c.1059+56C>T	NM_000155.3	rs111033821
NDP	ChrX:43818099	c.-207-1G>A	NM_000266.3	
NDP	ChrX:43832545	c.-208+5G>A	NM_000266.3	
NDP	ChrX:43832548	c.-208+2T>G	NM_000266.3	

NDP	ChrX:43832549	c.-208+1G>A	NM_000266.3	
NDP	ChrX:43832685	c.-343A>G	NM_000266.3	rs895911086
NDP	ChrX:43832722	c.-391_-380delCTCTCTCTCCCTinsGTCTCTC	NM_000266.3	
NDP	ChrX:43832724	c.-396_-383delTCCCTCTCTCTCTC	NM_000266.3	rs770996360
NF2	Chr22:30050946	c.516+232G>A	NM_000268.3	
OCRL	ChrX:128674707	c.40-14A>G	NM_000276.3	
OCRL	ChrX:128687279	c.239-4023A>G	NM_000276.3	
OCRL	ChrX:128696350	c.940-11G>A	NM_000276.3	
PAX6	Chr11:31685945	c.*125537G>T	NM_000280.4	rs606231388
PAX6	Chr11:31812434	c.1033-42_1033-26delATGTGTTCCTCAGTAACinsG	NM_000280.4	
PAX6	Chr11:31816377	c.524-41T>G	NM_000280.4	
PAX6	Chr11:31823338	c.142-14C>G	NM_000280.4	rs1131692291
PAX6	Chr11:31828391	c.-52+5delG	NM_000280.4	
PAX6	Chr11:31828391	c.-52+3_-52+6delAAGTinsTG	NM_000280.4	
PAX6	Chr11:31828392	c.-52+3_-52+4delAA	NM_000280.4	
PAX6	Chr11:31828395	c.-52+1delG	NM_000280.4	
PAX6	Chr11:31828396	c.-52+1G>A	NM_000280.4	
PAX6	Chr11:31828456	c.-115_-112delACTA	NM_000280.4	rs1011844558
PAX6	Chr11:31828461	c.-118_-117delTT	NM_000280.4	
PAX6	Chr11:31828469	c.-125dupG	NM_000280.4	
PAX6	Chr11:31828474	c.-128-1G>T	NM_000280.4	
PAX6	Chr11:31828474	c.-128-2delA	NM_000280.4	rs1131692282
PAX6	Chr11:31832372	c.-138_-129+3delCCTCATAAAGGTG	NM_000280.4	
PAX6	Chr11:31832374	c.-129+2T>A	NM_000280.4	
PAX6	Chr11:31832375	c.-129+1G>A	NM_000280.4	
SIL1	Chr5:138283180	c.1030-18G>A	NM_022464.4	rs769052639
WFS1	Chr4:6271704	c.-43G>T	NM_006005.3	
WRN	Chr8:30966107	c.2089-3024A>G	NM_000553.4	rs281865157
WRN	Chr8:30999982	c.3234-160A>G	NM_000553.4	

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
- ~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

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 detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (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.

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 and regulatory 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. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. 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 including, 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, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the 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 cornerstone of clinical interpretation and resulting patient management decisions. Our classifications follow the ACMG guideline 2015.

The final step in the analysis is orthogonal confirmation. Sequence and copy number variants classified as pathogenic, likely pathogenic, and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing or by orthogonal methods such as qPCR/ddPCR when they do not meet our stringent NGS quality metrics for a true positive call.

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, abstracts, and variant databases used to help ordering providers 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. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. 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 healthcare provider at no additional cost, according to our latest follow-up reporting policy.

CPT code(s) *

81403, 81404, 81405 x3, 81406 x3, 81408, 81479, 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

- American Academy of Ophthalmology - Cataracts

- Deng H. & Yuan L. 2014 Molecular genetics of congenital nuclear cataract. Eur J Med Genet. 2014 Feb;57(2-3):113-22.
- GeneReviews - Oculocerebrorenal syndrome
- Lowe Syndrome Trust
- NORD - COFS
- NORD - Cataract
- NORD - Nance-Horan Syndrome
- NORD - Oculocerebrorenal Syndrome
- National Eye Institute
- Royal National Institute of Blind People