Blueprint Genetics

Lysosomal Disorders and Mucopolysaccharidosis Panel

Test code: ME1501

Is a 102 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a clinical suspicion of lysosomal storage diseases (LSDs), mucolipidoses, mucopolysaccharidoses, glycoprotein storage disorders or lipid storage disorders. The genes on this panel are included in the Comprehensive Metabolism Panel.

About Lysosomal Disorders and Mucopolysaccharidosis

About fifty different lysosomal storage diseases (LSDs) have been identified. These disorders are caused by mutations that result in the deficiency or reduced activity of intracellular enzymes that catabolize biological macromolecules. LSDs are caused by lysosomal dysfunction as the result of a single enzyme deficiency required for the metabolism of lipids, glycoproteins or mucopolysaccharides. These absence or impaired effectiveness of these enzymes results in accumulation of specific macromolecular compounds within lysosomes in various tissues and organs, causing progressive damage that can become life-threatening in some diseases. Although each LSD is individually rare, as a group they have an incidence of about 1/7,000-8,000 live births, varying between different populations. LSDs may be variably expressed as infantile, juvenile, or adult forms. In adult-onset diseases, the pathogenesis is usually slower than in the infantile or juvenile forms, and may include peripheral and CNS symptoms, whereas infantile and juvenile forms often involve progressive central nervous system involvement in addition to peripheral symptoms. LSDs exhibit clinical heterogeneity. Symptomatic pathology may be a function of mutation type and residual enzyme levels and specific mutations or types of mutations may be connected to discrete disease effects even if genotype-phenotype correlations are not strong. Most of LSDs are autosomal recessively inherited, however a few are X-linked recessively inherited, such as Fabry disease and Hunter syndrome (MPS2). Other examples of LSDs covered by this panel are Gaucher's disease (the most common LSD), Tay-Sachs disease, Type II Pompe Disease, Salla disease, Krabbe disease and Hurler disease. Enzyme-replacement therapy (ERT) is now commercially available for six LSDs, typically used lifelong with specific management practices for each.

Availability

4 weeks

Gene Set Description

Genes in the Lysosomal Disorders and Mucopolysaccharidosis Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCC8	Hyperinsulinemic hypoglycemia, Diabetes, permanent neonatal, Hypoglycemia, leucine-induced, Diabetes mellitus, transient neonatal, Pulmonary arterial hypertension (PAH)	AD/AR	170	641
ACY1	Aminoacylase 1 deficiency	AR	5	14
ADAMTSL2*,#	Geleophysic dysplasia 3	AR	8	28
ADSL	Adenylosuccinase deficiency	AR	24	57
AGA	Aspartylglucosaminuria	AR	48	37
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	AR	16	70
ALDH7A1	Epilepsy, pyridoxine-dependent	AR	52	123
AMT	Glycine encephalopathy	AR	42	95

ANTXR2	Hyalinosis, infantile systemic, Fibromatosis, juveline hyaline	AR	17	47
ARG1	Hyperargininemia	AR	28	54
ARSA	Metachromatic leukodystrophy	AR	113	246
ARSB	Mucopolysaccharidosis (Maroteaux-Lamy)	AR	118	201
ASAH1	Spinal muscular atrophy with progressive myoclonic epilepsy, Farber lipogranulomatosis	AR	16	71
ASPA	Aspartoacylase deficiency (Canavan disease)	AR	54	102
ATP13A2	Parkinson disease (Kufor-Rakeb syndrome)	AR	21	40
BTD	Biotinidase deficiency	AR	170	247
CLN3	Neuronal ceroid lipofuscinosis, type 3	AR	100	72
CLN5	Neuronal ceroid lipofuscinosis, type 5	AR	62	47
CLN6	Neuronal ceroid lipofuscinosis, type 6	AR	41	83
CLN8	Neuronal ceroid lipofuscinosis, type 8	AR	45	44
COL11A2	Weissenbacher-Zweymuller syndrome, Deafness, Otospondylomegaepiphyseal dysplasia, Fibrochondrogenesis, Stickler syndrome type 3 (non-ocular)	AD/AR	29	57
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
CTNS	Cystinosis	AR	76	148
CTSA	Galactosialidosis	AR	17	38
CTSC	Periodontitis, juvenile, Haim-Munk syndrome, Papillon-Lefevre syndrome	AR	19	92
CTSD	Ceroid lipofuscinosis, neuronal	AR	12	18
CTSK	Pycnodysostosis	AR	35	58
DHCR7	Smith-Lemli-Opitz syndrome	AR	88	217
DPYD	5-fluorouracil toxicity, Developmental delay with or without dysmorphic facies and autism	AD/AR	62	86
DYM	Dyggve-Melchior-Clausen dysplasia, Smith-McCort dysplasia	AR	22	34
ETFA	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	8	29
ETFB	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	6	15
ETFDH	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	43	190

FH	Hereditary leiomyomatosis and renal cell cancer	AD/AR	178	207
FOLR1	Cerebral folate deficiency	AR	10	28
FUCA1	Fucosidosis	AR	19	33
GAA	Glycogen storage disease	AR	193	573
GALC	Krabbe disease	AR	107	243
GALNS	Mucopolysaccharidosis (Morquio syndrome)	AR	53	334
GAMT	Guanidinoacetate methyltransferase deficiency	AR	18	58
GBA*	Gaucher disease	AR	84	488
GCDH	Glutaric aciduria	AR	90	241
GLA	Fabry disease	XL	226	937
GLB1	GM1-gangliosidosis, Mucopolysaccharidosis (Morquio syndrome)	AR	90	220
GLDC	Glycine encephalopathy	AR	139	425
GM2A	GM2-gangliosidosis, AB variant	AR	10	12
GNE	Proximal myopathy and ophthalmoplegia, Nonaka myopathy, Sialuria	AD/AR	78	214
GNPTAB	Mucolipidosis	AR	166	184
GNPTG	Mucolipidosis	AR	45	46
GNS	Mucopolysaccharidosis (Sanfilippo syndrome)	AR	7	25
GPC3	Simpson-Golabi-Behmel syndrome	XL	33	75
GUSB*	Mucopolysaccharidosis	AR	27	62
HEXA	Tay-Sachs disease, GM2-gangliosidosis, Hexosaminidase A deficiency	AR	128	194
HEXB	Sandhoff disease	AR	55	120
HGSNAT	Mucopolysaccharidosis (Sanfilippo syndrome), Retinitis pigmentosa	AR	43	72
HRAS	Costello syndrome, Congenital myopathy with excess of muscle spindles	AD	43	31
HYAL1	Mucopolysaccharidosis	AR	2	3
IDS*	Mucopolysaccharidosis	XL	85	637
IDUA	Mucopolysaccharidosis	AR	105	282
L2HGDH	L-2-hydroxyglutaric aciduria	AR	15	79
LAMA2	Muscular dystrophy, congenital merosin-deficient	AR	199	301
LAMP2	Danon disease	XL	62	101
LDB3	Dilated cardiomyopathy (DCM), Myopathy, myofibrillar	AD	9	14

LIPA	Wolman disease, Cholesterol ester storage disease	AR	27	93
MAN1B1	Mental retardation	AR	8	26
MAN2B1	Mannosidosis, alpha B, lysosomal	AR	63	149
MANBA	Mannosidosis, lysosomal	AR	16	19
MCOLN1	Mucolipidosis	AR	52	36
MFSD8	Ceroid lipofuscinosis, neuronal	AR	27	47
MOCS1*	Molybdenum cofactor deficiency	AR	7	35
MOCS2	Molybdenum cofactor deficiency	AR	10	16
MYOT	Myopathy, myofibrillar, Muscular dystrophy, limb-girdle, 1A, Myopathy, spheroid body	AD	6	16
NAGA	Kanzaki disease, Alpha-n-acetylgalactosaminidase deficiency, Schindler disease type I, Schindler disease type III	AR	7	10
NAGLU	Mucopolysaccharidosis (Sanfilippo syndrome), Charcot-Marie-Tooth disease, axonal, type 2V	AR	74	171
NEU1	Sialidosis	AR	22	62
NPC1	Niemann-Pick disease	AR	164	472
NPC2	Niemann-pick disease	AR	21	27
PEX1	Heimler syndrome, Peroxisome biogenesis factor disorder 1A, Peroxisome biogenesis factor disorder 1B	AR	112	134
PEX10	Adrenoleukodystrophy, neonatal, Zellweger syndrome, Peroxisome biogenesis disorder, Ataxia	AR	34	29
PEX12	Zellweger syndrome, Peroxisome biogenesis disorder	AR	43	37
PEX13	Adrenoleukodystrophy, neonatal, Zellweger syndrome, Peroxisome biogenesis disorder	AR	9	10
PEX16	Zellweger syndrome, Peroxisome biogenesis disorder	AR	8	13
PEX26	Adrenoleukodystrophy, neonatal, Zellweger syndrome, Peroxisome biogenesis disorder	AR	13	27
PEX3	Zellweger syndrome, Peroxisome biogenesis disorder	AR	4	10
PEX5	Adrenoleukodystrophy, neonatal, Rhizomelic chondrodysplasia punctata, Zellweger syndrome, Peroxisome biogenesis disorder	AR	8	14
PEX6	Heimler syndrome, Peroxisome biogenesis disorder 4A, Peroxisome biogenesis disorder 4B	AR	58	107
PGK1	Phosphoglycerate kinase 1 deficiency	XL	16	26
PHYH	Refsum disease	AR	12	36
PPT1*	Ceroid lipofuscinosis, neuronal	AR	94	77

PRODH*	Hyperprolinemia	AR	52	10
PSAP	Krabbe disease, atypical, Metachromatic leukodystrophy due to saposin-b deficiency, Combined saposin deficiency, Gaucher disease, atypical, due to saposin C deficiency	AR	18	26
QDPR	Hyperphenylalaninemia, BH4-deficient	AR	14	66
RAI1	Smith-Magenis syndrome	AD	37	112
SGSH	Mucopolysaccharidosis (Sanfilippo syndrome)	AR	55	148
SLC17A5	Sialuria, Finnish (Salla disease), Infantile sialic acid storage disorder	AR	52	54
SLC25A15*	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	AR	24	36
SLC46A1	Folate malabsorption	AR	17	23
SMPD1	Niemann-Pick disease	AR	110	249
SUMF1	Multiple sulfatase deficiency	AR	21	53
SUOX	Sulfocysteinuria	AR	8	29
TCF4	Corneal dystrophy, Fuchs endothelial, Pitt-Hopkins syndrome	AD	105	146
TPP1	Spinocerebellar ataxia, Neuronal ceroid lipofuscinosis type 2	AR	75	112

*

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
ABCC8	Chr11:17415959	c.4412-13G>A	NM_000352.3	rs1008906426

ABCC8	Chr11:17427028	c.3399+13G>A	NM_000352.3	rs182340196
ABCC8	Chr11:17449501	c.2041-12C>A	NM_000352.3	
ABCC8	Chr11:17449510	c.2041-21G>A	NM_000352.3	rs746714109
ABCC8	Chr11:17449514	c.2041-25G>A	NM_000352.3	
ABCC8	Chr11:17452526	c.1672-20A>G	NM_000352.3	
ABCC8	Chr11:17465872	c.1333-1013A>G	NM_000352.3	
ABCC8	Chr11:17470268	c.1177-53_1177-51delGTG	NM_000352.3	rs1271038564
ABCC8	Chr11:17498513	c.-190C>G	NM_000352.3	
ADSL	Chr22:40742514	c.-49T>C	NM_000026.2	
AMT	Chr3:49459938	c.-55C>T	NM_000481.3	rs386833677
ARG1	Chr6:131901748	c.306-611T>C	NM_000045.3	
ARSA	Chr22:51064121	c.1108-12C>G	NM_000487.5	rs757806374
ARSA	Chr22:51064129	c.1108-20A>G	NM_000487.5	
BTD	Chr3:15683399	c.310-15delT	NM_000060.2	rs587783008
BTD	Chr3:15687154	c.*159G>A	NM_000060.2	rs530872564
CLN3	Chr16:28493392	c.1056+34C>A	NM_000086.2	
CLN3	Chr16:28497984	c.461-13G>C	NM_000086.2	rs386833721
CLN6	Chr15:68506515	c.297+113G>C	NM_017882.2	
COL2A1	Chr12:48379984	c.1527+135G>A	NM_001844.4	
CTNS	Chr17:3539712	c.-643_-642insT	NM_004937.2	
CTNS	Chr17:3543481	c.-19-1G>A	NM_001031681.2	
CTNS	Chr17:3552117	c.141-24T>C	NM_001031681.2	
CTNS	Chr17:3563518	c.971-12G>A	NM_001031681.2	rs375952052
CTSC	Chr11:88070895	c.-55C>A	NM_001814.4	rs766114323
CTSK	Chr1:150778521	c.244-29A>G	NM_000396.3	
ETFDH	Chr4:159593534	c.-75A>G	NM_004453.2	
ETFDH	Chr4:159602711	c.176-636C>G	NM_004453.2	
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	
GALC	Chr14:88401064	c.*12G>A	NM_000153.3	rs372641636
GALC	Chr14:88459574	c.-66G>C	NM_000153.3	rs146439771
GALC	Chr14:88459575	c.-67T>G	NM_000153.3	rs571945132
GALC	Chr14:88459917	c.-74T>A	NM_001201402.1	
GALC	Chr14:88459971	c.-128C>T	NM_001201402.1	rs181956126
GALNS	Chr16:88898676	c.899-167A>G	NM_000512.4	
GALNS	Chr16:88908390	c.245-11C>G	NM_000512.4	
GAMT	Chr19:1399508	c.391+15G>T	NM_138924.2	rs367567416
GBA	Chr1:155205646	c.1225-14_1225-11delTGTCinsAGT	NM_000157.3	
GBA	Chr1:155208109	c.589-12C>G	NM_000157.3	
GBA	Chr1:155211053	c.-150A>G	NM_000157.3	rs1232943445
GCDH	Chr19:13010271	c.1244-11A>G	NM_000159.3	
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	
GNPTAB	Chr12:102159106	c.1613-25delA	NM_024312.4	rs777271928
GNPTG	Chr16:1412562	c.610-16_609+28del	NM_032520.4	rs193302853
HEXA	Chr15:72640009	c.1146+18A>G	NM_000520.4	
HEXB	Chr5:74014605	c.1243-17A>G	NM_000521.3	
HEXB	Chr5:74016442	c.1509-26G>A	NM_000521.3	rs201580118
HEXB	Chr5:74016585	c.1613+15_1613+18dupAAGT	NM_000521.3	rs779273534
HEXB	Chr5:74016926	c.1614-16_1615dupTTCATGTTATCTACAGAC	NM_000521.3	rs756912360
HEXB	Chr5:74016929	c.1614-14C>A	NM_000521.3	rs201448394
HGSNAT	Chr8:43028824	c.821-28_821-10delTTGCTTATGCTTTGTACTT	NM_152419.2	
IDS	ChrX:148564764	c.1181-15C>A	NM_000202.5	

IDS	ChrX:148568762	c.*57A>G	NM_006123.4	
IDS	ChrX:148578704	c.709-657G>A	NM_000202.5	
L2HGDH	Chr14:50735527	c.906+354G>A	NM_024884.2	
LAMA2	Chr6:129633984	c.3175-22G>A	NM_000426.3	rs777129293
LAMA2	Chr6:129636608	c.3556-13T>A	NM_000426.3	rs775278003
LAMA2	Chr6:129714172	c.5235-18G>A	NM_000426.3	rs188365084
LAMA2	Chr6:129835506	c.8989-12C>G	NM_000426.3	rs144860334
MOCS1	Chr6:39874534	c.*365_*366delAG	NM_005943.5	rs397518419
MOCS1	Chr6:39876810	c.*7+6T>C	NM_005943.5	
MOCS1	Chr6:39894006	c.251-418delT	NM_005943.5	
NPC1	Chr18:21132700	c.1554-1009G>A	NM_000271.4	
NPC1	Chr18:21137182	c.882-28A>G/T	NM_000271.4	
NPC1	Chr18:21137182	c.882-28A>G	NM_000271.4	
NPC1	Chr18:21137182	c.882-28A>T	NM_000271.4	
PEX6	Chr6:42933858	c.2301-15C>G	NM_000287.3	rs267608236
PEX6	Chr6:42933952	c.2300+28G>A	NM_000287.3	rs267608237
PGK1	ChrX:77381262	c.1214-25T>G	NM_000291.3	
PPT1	Chr1:40539203	c.*526_*529delATCA	NM_000310.3	rs386833624
PPT1	Chr1:40558194	c.125-15T>G	NM_000310.3	rs386833629
PSAP	Chr10:73583679	c.778-26C>A	NM_001042465.1	
QDPR	Chr4:17500790	c.436+2552A>G	NM_000320.2	
SGSH	Chr17:78190802	c.249+27_249+28delGG	NM_000199.3	
SMPD1	Chr11:6415102	c.1341-21_1341-18delAATG	NM_000543.4	rs1312743513
TPP1	Chr11:6637752	c.887-18A>G	NM_000391.3	

Test Strengths

All exons of the *GBA* gene have segmentally duplicated pseudogenes that reduce sensitivity of NGS diagnostics in general. However, Blueprint Genetics custom assay has good coverage (>20x) with high mapping rates (mapping quality >40) for 100.0% of the target regions in *GBA* gene. Our validation showed high mean coverage of 184X for the *GBA* gene. Thus, our NGS Panel is not expected to have major limitations in detecting variants in *GBA* gene although clinical validation has not been performed at large scale for Gaucher disease.

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: *ADAMTSL2* (NM_014694:11-19). 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 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 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 corner stone 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 health care provider at no additional cost.

CPT code(s) *

81404 x3, 81405 x9, 81406 x10, 81407, 81479

* 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

- GeneReviews - Fabry Disease
- GeneReviews - Fabry Disease.
- GeneReviews - Gaucher Disease
- GeneReviews - Hunter Syndrome

- GeneReviews - Hurler Disease
- GeneReviews - Krabbe Disease
- GeneReviews - Mucopolysaccharidosis Type I
- GeneReviews - Mucopolysaccharidosis Type II.
- GeneReviews - Pompe Disease
- GeneReviews - Pompe Disease.
- Hide & Seek Foundation for Lysosomal Disease Research
- International Advocate for Glycoprotein Storage Diseases
- Lysosomal Disease Network
- Lysosomal Storage Disorders Support Society
- National Fabry Disease Foundation
- National Gaucher Foundation
- National MPS Society
- National Niemann-Pick Disease Foundation
- National Organization for Rare Disorders
- National Tay-Sachs and Allied Diseases Association
- Society for Mucopolysaccharide Diseases
- United Pompe Foundation