Blueprint Genetics

# Comprehensive Hearing Loss and Deafness Panel

**Test code: EA0501**

Is a 239 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 of syndromic or non-syndromic genetic hearing loss.

Hearing loss is a genetically and clinically heterogenous group of diseases and syndromes and may be classified in several different ways. This Panel includes comprehensively genes associated with both syndromic and non-syndromic hearing loss. In addition to protein coding regions, two disease causing intronic variants of *HGF* gene are targeted in this Panel. Inheritance of these disorders may be autosomal recessive or dominant as well as X-linked. This comprehensive Panel includes Waardenburg Syndrome Panel, Pendred Syndrome Panel, Usher Syndrome Panel, Stickler Syndrome Panel, Alport Syndrome Panel, Branchio-Oto-Renal Panel, Syndromic Hearing Loss Panel and Non-Syndromic Hearing Loss Panel.

## About Comprehensive Hearing Loss and Deafness

Hearing loss is a genetically very heterogenous group of phenotypes varying in severity and causes. Non-syndromic sensorineural hearing loss is a partial or total loss of hearing that occurs without other associated clinical findings. In syndromic hearing loss, symptoms affecting other parts of the body occur in addition to hearing impairment or deafness. Sensorineural hearing loss can be unilateral or bilateral and it can be stable or progressive. In addition, the loss may appear with various intensivity to high, middle or low tones. It is estimated that approximately 60-80% of congenital hearing loss is genetic in origin. Some 60%-to-70% of congenital hereditary hearing impairnment have a non-syndromic origin. The prevalence of non-syndromic hearing loss is 3-4:10,000 neonates and increases with age. In many populations, mutations in *GJB2* are the most prevalent explaining up to 50% of all non-syndromic hearing losses. Altogether syndromic hearing loss accounts for 20% to 30% of congenital hearing loss and deafness and the combined prevalence of syndromic hearing loss is approximately 1-2:10,000.

## Availability

Results in 3-4 weeks

## Gene set description

Genes in the Comprehensive Hearing Loss and Deafness Panel and their clinical significance

| Gene | Associated phenotypes | Inheritance | ClinVar | HGMD |
|---|---|---|---|---|
| ABHD12 | Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract | AR | 16 | 20 |
| ACTG1* | Deafness, Baraitser-Winter syndrome | AD | 27 | 47 |
| ADCY1 | Deafness | AR | 1 | 1 |
| ADGRV1 | Febrile seizures, familial, 4, Usher syndrome, type IIC | AR | 71 | 236 |
| AIFM1 | Deafness, Combined oxidative phosphorylation deficiency 6, Cowchock syndrome | XL | 27 | 31 |
| ALMS1* | Alström syndrome | AR | 197 | 302 |
| ANKH | Calcium pyrophosphate deposition disease (familial chondrocalcinosis type 2), Craniometaphyseal dysplasia autosomal dominant type | AD | 13 | 20 |

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|---|---|---|---|---|
| ARSG | Usher syndrome, type IV | AR | 1 | 1 |
| ATP2B2 | Sensorineural hearing loss | AD | 3 | 7 |
| ATP6V1B1 | Renal tubular acidosis with deafness | AR | 15 | 56 |
| ATP6V1B2 | Deafness, congenital, with onychodystrophy, autosomal dominant, Zimmermann-Laband syndrome 2 | AD | 6 | 3 |
| BCS1L | Bjornstad syndrome, GRACILE syndrome, Leigh syndrome, Mitochondrial complex III deficiency, nuclear type 1 | AR | 42 | 37 |
| BDP1* | Hearing loss | AD/AR | 1 | 1 |
| BSND | Sensorineural deafness with mild renal dysfunction, Bartter syndrome | AR | 10 | 20 |
| BTD | Biotinidase deficiency | AR | 170 | 247 |
| C10ORF2 | Perrault syndrome, Mitochondrial DNA depletion syndrome, Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 3 | AD/AR | 37 | 80 |
| CABP2 | Deafness | AR | 1 | 6 |
| CACNA1D | Primary aldosteronism, seizures, and neurologic abnormalities, Sinoatrial node dysfunction and deafness | AD/AR | 7 | 8 |
| CATSPER2 | Male Infertility, Deafness | AR | 2 | 7 |
| CCDC50 | Deafness | AD | 1 | 4 |
| CD151 | Raph blood group, Nephropathy with pretibial epidermolysis bullosa and deafness | AR | 1 | 3 |
| CD164 | Deafness, autosomal dominant 66 | AD | 1 | 1 |
| CDC14A | Deafness, autosomal recessive 105 | AR | 7 | 9 |
| CDC42 | Takenouchi-Kosaki syndrome, Noonan-syndrome like phenotype | AD | 11 | 9 |
| CDH23 | Deafness, Usher syndrome, type 1D | AR | 94 | 358 |
| CDK9 | | AR | | 1 |
| CDKN1C | Beckwith-Wiedemann syndrome, IMAGE syndrome | AD | 35 | 81 |
| CEACAM16 | Deafness | AD/AR | 4 | 4 |
| CEP250 | Cone rod dystrophy and hearing loss | AR | | 5 |
| CEP78 | Cone rod dystrophy and hearing loss | AR | 7 | 9 |
| CHD7 | Isolated gonadotropin-releasing hormone deficiency, CHARGE syndrome | AD | 276 | 860 |
| CHSY1 | Temtamy preaxial brachydactyly syndrome | AR | 6 | 16 |
| CIB2 | Deafness, Usher syndrome type IJ | AR | 5 | 18 |
| CLDN14 | Deafness | AR | 11 | 12 |

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|---|---|---|---|---|
| CLIC5 | Deafness | AR | 1 | 2 |
| CLPP | Deafness | AR | 4 | 13 |
| CLRN1 | Retinitis pigmentosa, Usher sydnrome, type 3A | AR | 24 | 39 |
| COCH | Deafness | AD | 14 | 29 |
| COL11A1 | Marshall syndrome, Fibrochondrogenesis, Stickler syndrome type 2 | AD/AR | 34 | 94 |
| 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 |
| COL4A3 | Alport syndrome, Hematuria, benign familial | AD/AR | 123 | 264 |
| COL4A4 | Alport syndrome | AD/AR | 110 | 232 |
| COL4A5 | Alport syndrome | XL | 704 | 992 |
| COL4A6 | Deafness, with cochlear malformation | XL | 11 | 5 |
| COL9A1 | Stickler syndrome recessive type, Multiple epiphyseal dysplasia type 6 (EDM6) | AD/AR | 9 | 6 |
| COL9A2 | Stickler syndrome, Multiple epiphyseal dysplasia type 2 (EDM2) | AD/AR | 7 | 12 |
| COL9A3 | Multiple epihyseal dysplasia type 3 (EDM3), Stickler syndrome recessive type | AD/AR | 10 | 14 |
| CRYM | Deafness | AD | 2 | 4 |
| DCAF17 | Woodhouse-Sakati syndrome | AR | 14 | 14 |
| DCDC2 | Deafness, Nephronophthisis, Sclerosing cholangitis, neonatal | AR | 13 | 9 |
| DFNA5 | Deafness | AD | 7 | 13 |
| DFNB31 | Deafness, Usher syndrome, type 2D | AR | 12 | 31 |
| DFNB59 | Deafness | AR | 12 | 20 |
| DIABLO | Deafness | AD | 1 | 2 |
| DIAPH1 | Deafness, Seizures, cortical blindness, and microcephaly syndrome (SCBMS) | AD/AR | 10 | 15 |
| DIAPH3 | Non-syndromic sensorineural deafness | AD | 1 | 9 |
| DLX5 | Split-hand/foot malformation with sensorineural hearing loss | AR | 3 | 9 |

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| DMXL2 | Deafness, autosomal dominant, 71, Polyendocrine-polyneuropathy syndrome, Epileptic encephalopathy, early infantile | AD/AR | 2 | 6 |
| DNMT1 | Neuropathy, hereditary sensory, Cerebellar ataxia, deafness, and narcolepsy | AD | 9 | 20 |
| DSPP | Dentin dysplasia, Dentinogenesis imperfecta, Deafness, with dentinogenesis imperfecta | AD | 11 | 53 |
| EDN3 | Hirschsprung disease, Central hypoventilation syndrome, congenital, Waardenburg syndrome | AD/AR | 7 | 21 |
| EDNRB | Hirschsprung disease, ABCD syndrome, Waardenburg syndrome | AD/AR | 12 | 66 |
| EIF3F | Intellectual disability | AR | | |
| ELMOD3 | Deafness | AR | 1 | 2 |
| EPS8 | Deafness | AR | 2 | 2 |
| EPS8L2 | Deafness, autosomal recessive 106 | AR | 2 | 2 |
| ESPN* | Deafness | AD/AR | 12 | 15 |
| ESRRB | Deafness | AR | 12 | 19 |
| EYA1 | Otofaciocervical syndrome, Branchiootic syndrome, Branchiootorenal syndrome | AD | 56 | 218 |
| EYA4 | Dilated cardiomyopathy (DCM), Deafness, autosomal dominant 10 | AD | 15 | 28 |
| FAM136A | Sensorineural hearing loss | AD | 1 | 2 |
| FAM65B | Deafness | AR | 1 | 2 |
| FDXR | Auditory neuropathy and optic atrophy | AR | 5 | 19 |
| FGF3 | Deafness, congenital with inner ear agenesis, microtia, and microdontia | AR | 13 | 20 |
| FGFR3 | Lacrimoauriculodentodigital syndrome, Muenke syndrome, Crouzon syndrome with acanthosis nigricans, Camptodactyly, tall stature, and hearing loss (CATSHL) syndrome, Achondroplasia, Hypochondroplasia, Thanatophoric dysplasia type 1, Thanatophoric dysplasia type 2, SADDAN | AD/AR | 54 | 77 |
| FITM2 | Dystonia, Deafness | AR | | 1 |
| FOXI1 | Pendred syndrome, Enlarged vestibular aqueduct | AR | 1 | 11 |
| GATA3 | Hypomagnesemia, renal | AD | 22 | 86 |
| GIPC3 | Deafness | AR | 9 | 20 |
| GJA1* | Oculodentodigital dysplasia mild type, Oculodentodigital dysplasia severe type, Syndactyly type 3 | AD/AR | 31 | 107 |
| GJB2 | Deafness, Bart-Pumphrey syndrome, Keratoderma, palmoplantar, with deafness, Vohwinkel syndrome, Hystrix-like ichthyosis with deafness, Keratitis-icthyosis-deafness syndrome | AD/AR/Digenic | 133 | 405 |

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|---|---|---|---|---|
| GJB3 | Deafness, Erythrokeratodermia variabilis et progressiva 1, Deafness, autosomal dominant 2B | AD/AR | 11 | 40 |
| GJB6 | Deafness, Deafness, autosomal dominant 3B, Ectodermal dysplasia, hidrotic (Clouston syndrome) | AD/AR | 10 | 33 |
| GPSM2 | Deafness, Chudley-McCullough syndrome | AR | 18 | 11 |
| GRHL2 | Ectodermal dysplasia/short stature syndrome, Deafness, autosomal dominant 28, Corneal dystrophy, posterior polymorphous | AD/AR | 12 | 12 |
| GRXCR1 | Deafness | AR | 8 | 9 |
| GRXCR2 | Deafness | AR | 1 | 2 |
| HARS* | Charcot-Marie-Tooth disease, axonal, type 2W, Usher syndrome, type 3B | AR | 6 | 12 |
| HARS2 | Perrault syndrome | AR | 7 | 3 |
| HGF | Deafness | AR | 4 | 10 |
| HOMER2 | Deafness | AD | 2 | 1 |
| HOXB1 | Facial paresis, hereditary congenital | AR | 3 | 6 |
| HSD17B4 | Perrault syndrome, D-bifunctional protein deficiency | AR | 60 | 99 |
| ILDR1 | Deafness | AR | 8 | 27 |
| KARS | Charcot-Marie-Tooth disease | AR | 9 | 23 |
| KCNE1 | Long QT syndrome, Jervell and Lange-Nielsen syndrome | AD/AR/Digenic | 11 | 46 |
| KCNJ10 | Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SESAME syndrome), Pendred syndrome, Enlarged vestibular aqueduct | AR/Digenic | 13 | 29 |
| KCNQ1 | Short QT syndrome, Long QT syndrome, Atrial fibrillation, Jervell and Lange-Nielsen syndrome | AD/AR/Digenic | 298 | 631 |
| KCNQ4 | Deafness | AD | 28 | 37 |
| KIT | Gastrointestinal stromal tumor, Piebaldism | AD | 79 | 116 |
| LARS2 | Perrault syndrome, Hydrops, lactic acidosis, and sideroblastic anemia (HLASA) | AR | 14 | 14 |
| LHFPL5 | Deafness | AR | 7 | 10 |
| LMX1A | Hearing loss | AD/AR | 1 | 4 |
| LOXHD1 | Deafness | AR | 26 | 60 |
| LRP2 | Donnai-Barrow syndrome, Facioculoacousticorenal syndrome | AR | 24 | 38 |
| LRTOMT | Deafness | AR | 7 | 17 |
| MAN2B1 | Mannosidosis, alpha B, lysosomal | AR | 63 | 149 |
| MANBA | Mannosidosis, lysosomal | AR | 16 | 19 |

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|---|---|---|---|---|
| MARVELD2 | Deafness | AR | 9 | 17 |
| MET | Deafness, Renal cell carcinoma, papillary, Osteofibrous dysplasia, susceptibility to | AD/AR | 20 | 34 |
| MGP | Keutel syndrome | AR | 5 | 8 |
| MIR96 | Deafness | AD | 2 | 4 |
| MITF | Tietz albinism-deafness syndrome, Waardenburg syndrome, Coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness (COMMAD) | AD/AR | 32 | 58 |
| MPZL2 | Sensorineural hearing loss | AR | | 4 |
| MSRB3 | Deafness | AR | 5 | 2 |
| 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 | 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 | |

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|---|---|---|---|---|
| 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 | | 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 | 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 | 3 | |
| MT-TW | Leigh syndrome, Myopathy, mitochondrial | Mitochondrial | 8 | |
| MT-TY | Mitochondrial multisystemic disorder | Mitochondrial | 4 | |
| MYH14 | Deafness, Peripheral neuropathy, myopathy, hoarseness, and hearing loss | AD | 7 | 44 |
| MYH9 | Sebastian syndrome, May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, Macrothrombocytopenia and progressive sensorineural deafness, Deafness, autosomal dominant 17 | AD | 25 | 117 |

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|---|---|---|---|---|
| MYO15A | Deafness | AR | 97 | 235 |
| MYO3A | Deafness | AR | 9 | 22 |
| MYO6 | Deafness, Deafness, autosomal dominant, 22 | AD/AR | 24 | 68 |
| MYO7A | Deafness, Deafness, autosomal dominant 11, Usher syndrome, type I | AD/AR | 239 | 515 |
| NARS2 | Combined oxidative phosphorylation deficiency | AR | 12 | 12 |
| NDP | Exudative vitreoretinopathy, Norrie disease | XL | 31 | 167 |
| NLRP3 | Neonatal onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome, Chronic infantile neurologic cutaneous articular (CINCA) syndrome, Familial cold-induced autoinflammatory syndrome 1 | AD | 20 | 136 |
| OSBPL2 | Deafness | AD | 2 | 3 |
| OTOA*,# | Deafness | AR | 19 | 28 |
| OTOF | Neuropathy, Deafness | AR | 107 | 163 |
| OTOG | Deafness | AR | 18 | 3 |
| OTOGL | Deafness | AR | 26 | 23 |
| P2RX2 | Deafness | AD | 2 | 4 |
| PAX3 | Craniofacial-deafness-hand syndrome, Waardenburg syndrome | AD/AR | 54 | 149 |
| PCDH15 | Deafness, Usher syndrome, type 1D | AR/Digenic | 113 | 118 |
| PDE1C | Hearing loss | AD | 2 | 2 |
| PDZD7 | Deafness, autosomal recessive | AR | 11 | 19 |
| PEX1 | Heimler syndrome, Peroxisome biogenesis factor disorder 1A, Peroxisome biogenesis factor disorder 1B | AR | 112 | 134 |
| PEX26 | Adrenoleukodystrophy, neonatal, Zellweger syndrome, Peroxisome biogenesis disorder | AR | 13 | 27 |
| PEX6 | Heimler syndrome, Peroxisome biogenesis disorder 4A, Peroxisome biogenesis disorder 4B | AR | 58 | 107 |
| PISD | | AR | | |
| PNPT1*,# | Deafness, Combined oxidative phosphorylation deficiency, 13 | AR | 11 | 13 |
| POLR1C | Treacher Collins syndrome | AR | 17 | 21 |
| POLR1D | Treacher Collins syndrome | AD/AR | 9 | 26 |
| POU3F4 | Deafness | XL | 25 | 80 |
| POU4F3 | Deafness | AD | 9 | 33 |
| PRPS1* | Phosphoribosylpyrophosphate synthetase I superactivity, Arts syndrome, Charcot-Marie-Tooth disease, X-linked recessive, 5, Deafness, X-linked 1 | XL | 27 | 32 |

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|---|---|---|---|---|
| RDX* | Deafness | AR | 6 | 10 |
| RMND1* | Combined oxidative phosphorylation deficiency | AR | 17 | 15 |
| RPS6KA3 | Coffin-Lowry syndrome, Mental retardation | XL | 65 | 171 |
| S1PR2 | Deafness, autosomal recessive 68 | AR | 2 | 3 |
| SALL1* | Townes-Brocks syndrome 1 | AD | 31 | 87 |
| SALL4 | Acro-renal-ocular syndrome, Duane-radial ray/Okohiro syndrome | AD | 21 | 56 |
| SEMA3E | CHARGE syndrome | AD | 1 | 4 |
| SERPINB6 | Deafness | AR | 2 | 3 |
| SIX1 | Deafness, Branchiootic syndrome, Branchiootorenal syndrome | AD | 11 | 19 |
| SIX5 | Branchiootorenal syndrome | AD | 3 | 10 |
| SLC17A8 | Deafness | AD | 1 | 8 |
| SLC19A2 | Thiamine-responsive megaloblastic anemia syndrome | AR | 14 | 51 |
| SLC22A4 | Hearing loss | AR | | 2 |
| SLC26A4 | Deafness, Pendred syndrome, Enlarged vestibular aqueduct | AR | 181 | 548 |
| SLC26A5 | Deafness | AR | 2 | 7 |
| SLC29A3 | Histiocytosis-lymphadenopathy plus syndrome, Dysosteosclerosis | AR | 17 | 25 |
| SLC33A1* | Congenital cataracts, hearing loss, and neurodegeneration, Spastic paraplegia 42, autosomal dominant | AD/AR | 6 | 7 |
| SLC52A2 | Brown-Vialetto-Van Laere syndrome | AR | 27 | 25 |
| SLC52A3 | Fazio-Londe disease, Brown-Vialetto-Van Laere syndrome | AR | 30 | 42 |
| SLITRK6 | Deafness and myopia | AR | 3 | 5 |
| SMAD4 | Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Polyposis, juvenile intestinal, Myhre dysplasia, Hereditary hemorrhagic telangiectasia | AD | 179 | 143 |
| SMPX | Deafness | XL | 8 | 14 |
| SNAI2 | Waardenburg syndrome, Piebaldism | AR | 2 | 4 |
| SOX10 | Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease, Kallmann syndrome | AD | 56 | 148 |
| SPATA5 | Developmental delay with or without dysmorphic facies and autism, Epilepsy, hearing loss, and mental retardation syndrome (EHLMRS) | AR | 27 | 27 |
| STAG2 | Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder | XL | 6 | 14 |
| STRC*,# | Deafness | AR | 31 | 85 |

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| SUCLA2 | Mitochondrial DNA depletion syndrome | AR | 9 | 29 |
| SUCLG1 | Mitochondrial DNA depletion syndrome | AR | 12 | 28 |
| SYNE4 | Deafness | AR | 6 | 2 |
| SYT2 | Myasthenic syndrome, congenital 7, presynaptic | AD | 3 | 3 |
| TBC1D24 | Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome, Deafness, autosomal dominant, 65, Myoclonic epilepsy, infantile, familial, Epileptic encephalopathy, early infantile, 16, Deafness, autosomal recessive 86 | AD/AR | 43 | 55 |
| TBL1X | Congenital hypothyroidism, Hearing loss | | 2 | 8 |
| TCOF1 | Treacher Collins syndrome | AD | 50 | 330 |
| TECTA | Deafness | AD/AR | 36 | 120 |
| TFAP2A | Branchiooculofacial sydrome | AD | 23 | 42 |
| TIMM8A* | Mohr-Tranebjaerg syndrome, Jensen syndrome, Opticoacoustic nerve atrophy with dementia | XL | 11 | 21 |
| TJP2 | Cholestasis, progressive familial intrahepatic, Hypercholanemia, familial, Deafness, autosomal dominant 51 | AD/AR | 25 | 27 |
| TMC1 | Deafness, Deafness, autosomal dominant 36 | AD/AR | 33 | 91 |
| TMEM132E | Hearing loss | AR | | 1 |
| TMIE | Deafness | AR | 9 | 10 |
| TMPRSS3 | Deafness | AR | 25 | 82 |
| TNC | Deafness | AD | 3 | 6 |
| TPRN | Deafness | AR | 6 | 12 |
| TRIOBP | Deafness | AR | 22 | 40 |
| TRMU | Liver failure, infantile, Reversible infantile respiratory chain deficiency | AR | 20 | 21 |
| TSHZ1 | Aural atresia, congenital | AD | 2 | 4 |
| TSPEAR* | Deafness | AR | 2 | 7 |
| TUBB4B | Leber congenital amaurosis, Hearing loss | AD | 2 | 3 |
| TYR* | Albinism, oculocutaneous | AR | 77 | 441 |
| USH1C | Deafness, Usher syndrome, type IC | AR | 45 | 51 |
| USH1G | Usher syndrome, type 1G | AR | 13 | 32 |
| USH2A | Retinitis pigmentosa 39, Usher syndrome, type 2A | AR | 401 | 1169 |
| VCAN | Wagner disease | AD | 11 | 19 |
| WBP2 | Deafness, autosomal recessive 107 | AR | 3 | 3 |

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|---|---|---|---|---|
| WFS1 | Wolfram syndrome, Deafness, Wolfram-like syndrome, autosomal dominant, Deafness, autosomal dominant 6/14/38, Cataract 41 | AD/AR | 69 | 362 |
| XYLT2 | Spondyloocular syndrome | AR | 2 | 10 |

*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 (#)

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 |
|---|---|---|---|---|
| AIFM1 | ChrX:129274636 | c.697-44T>G | NM_004208.3 | |
| AIFM1 | ChrX:129299753 | c.-123G>C | NM_004208.3 | rs724160014 |
| ANKH | Chr5:14871567 | c.-11C>T | NM_054027.4 | |
| BCS1L | Chr2:219524871 | c.-147A>G | NM_004328.4 | |
| BCS1L | Chr2:219525123 | c.-50+155T>A | NM_004328.4 | rs386833855 |
| BTD | Chr3:15683399 | c.310-15delT | NM_000060.2 | rs587783008 |
| BTD | Chr3:15687154 | c.*159G>A | NM_000060.2 | rs530872564 |
| CDKN1C | Chr11:2905209 | c.*5+20G>T | NM_000076.2 | rs760540648 |
| CHD7 | Chr8:61734568 | c.2836-15C>G | NM_017780.3 | |
| CHD7 | Chr8:61757794 | c.5051-15T>A | NM_017780.3 | |
| CHD7 | Chr8:61763034 | c.5405-18C>A | NM_017780.3 | rs199981784 |
| CHD7 | Chr8:61763035 | c.5405-17G>A | NM_017780.3 | rs794727423 |
| CHD7 | Chr8:61763039 | c.5405-13G>A | NM_017780.3 | rs1131690787 |
| CLRN1 | Chr3:150660197 | c.254-649T>G | NM_001195794.1 | rs976853535 |
| 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 | |

| | | | | |
|---|---|---|---|---|
| COL4A3 | Chr2:228145145 | c.2224-11C>T | NM_000091.4 | |
| COL4A3 | Chr2:228168708 | c.4028-27A>G | NM_000091.4 | |
| COL4A3 | Chr2:228173092 | c.4462+457C>G | NM_000091.4 | |
| COL4A3 | Chr2:228173596 | c.4463-18dupA | NM_000091.4 | rs769590145 |
| COL4A4 | Chr2:227875240 | c.4334-23A>G | NM_000092.4 | |
| COL4A5 | ChrX:107813924 | c.385-719G>A | NM_033380.2 | rs104886396 |
| COL4A5 | ChrX:107816792 | c.466-12G>A | NM_033380.2 | rs104886414 |
| COL4A5 | ChrX:107820077 | c.609+875G>T | NM_033380.2 | |
| COL4A5 | ChrX:107821295 | c.646-12_646-11delTT | NM_033380.2 | rs104886436 |
| COL4A5 | ChrX:107834930 | c.1423+57dupC | NM_033380.2 | rs104886328 |
| COL4A5 | ChrX:107838719 | c.1424-20T>A | NM_033380.2 | rs281874668 |
| COL4A5 | ChrX:107842994 | c.1948+894C>G | NM_033380.2 | |
| COL4A5 | ChrX:107845097 | c.2042-18A>G | NM_033380.2 | rs104886341 |
| COL4A5 | ChrX:107849932 | c.2245-40A>G | NM_033380.2 | |
| COL4A5 | ChrX:107849958 | c.2245-14T>A | NM_033380.2 | |
| COL4A5 | ChrX:107852872 | c.2395+2750A>G | NM_033380.2 | |
| COL4A5 | ChrX:107908726 | c.3374-11C>A | NM_033380.2 | rs104886387 |
| COL4A5 | ChrX:107933678 | c.4529-2300T>G | NM_033380.2 | |
| COL4A5 | ChrX:107935633 | c.4529-345A>G | NM_033380.2 | |
| COL4A5 | ChrX:107938272 | c.4821+121T>C | NM_033380.2 | rs104886423 |
| COL4A5 | ChrX:107938337 | c.4822-152dupT | NM_033380.2 | |
| COL4A5 | ChrX:107938346 | c.4822-151_4822-150insT | NM_033380.2 | rs397515494 |
| DCAF17 | Chr2:172305176 | c.322-14delC | NM_025000.3 | rs201494527 |
| DFNA5 | Chr7:24746007 | c.991-15_991-13delTTC | NM_004403.2 | rs727505273 |
| DIAPH3 | Chr13:60738072 | c.-172G>A | NM_001042517.1 | |
| DIAPH3 | Chr13:60738073 | c.-173C>T | NM_001042517.1 | |
| EDN3 | Chr20:57875743 | c.-125G>A | NM_000114.2 | |
| EDN3 | Chr20:57875849 | c.-19C>A | NM_000114.2 | rs375594972 |
| EYA1 | Chr8:72156939 | c.1051-12T>G | NM_000503.4 | |
| EYA1 | Chr8:72211483 | c.640-15G>A | NM_000503.4 | |
| EYA4 | Chr6:133833847 | c.1282-12T>A | NM_004100.4 | |

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|---|---|---|---|---|
| EYA4 | Chr6:133833997 | c.1341-19T>A | NM_004100.4 | |
| GJB2 | Chr13:20763744 | c.-22-2A>C | NM_004004.5 | rs201895089 |
| GJB2 | Chr13:20766920 | c.-23+2T>A | NM_004004.5 | |
| GJB2 | Chr13:20766921 | c.-23+1G>A | NM_004004.5 | rs80338940 |
| GJB2 | Chr13:20766922 | c.-23G>T | NM_004004.5 | rs786204734 |
| GJB2 | Chr13:20767158 | c.-259C>T | NM_004004.5 | |
| GJB2 | Chr13:20767159 | c.-260C>T | NM_004004.5 | |
| GRHL2 | Chr8:102505149 | c.20+133delA | NM_024915.3 | |
| GRHL2 | Chr8:102505272 | c.20+257delT | NM_024915.3 | |
| GRHL2 | Chr8:102505561 | c.20+544G>T | NM_024915.3 | |
| GRXCR1 | Chr4:42965170 | c.627+19A>T | NM_001080476.2 | rs201824235 |
| HGF | Chr7:81384504 | c.482+1991_482+2000delGATGATGAAA | NM_000601.4 | rs900334407 |
| HGF | Chr7:81384516 | c.482+1986_482+1988delTGA | NM_000601.4 | |
| HSD17B4 | Chr5:118837725 | c.1285-11C>G | NM_001199291.1 | rs779466683 |
| KCNJ10 | Chr1:160039811 | c.-1+1G>T | NM_002241.4 | rs796052606 |
| KCNQ1 | Chr11:2484803 | | | rs2074238 |
| MYO3A | Chr10:26409593 | c.1777-12G>A | NM_017433.4 | |
| MYO6 | Chr6:76593963 | c.2417-1758T>G | NM_004999.3 | |
| MYO7A | Chr11:76839534 | c.-48A>G | NM_000260.3 | |
| MYO7A | Chr11:76893448 | c.3109-21G>A | NM_000260.3 | |
| MYO7A | Chr11:76915107 | c.5327-14T>G | NM_000260.3 | |
| MYO7A | Chr11:76915110 | c.5327-11A>G | NM_000260.3 | rs397516316 |
| MYO7A | Chr11:76919448 | c.5857-27_5857-26insTTGAG | NM_000260.3 | |
| 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 |
| PAX3 | Chr2:223085913 | c.958+28A>T | NM_181459.3 | |

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|---|---|---|---|---|
| PCDH15 | Chr10:56560684 | c.-29+1G>C | NM_001142763.1 | |
| PEX6 | Chr6:42933858 | c.2301-15C>G | NM_000287.3 | rs267608236 |
| PEX6 | Chr6:42933952 | c.2300+28G>A | NM_000287.3 | rs267608237 |
| RPS6KA3 | ChrX:20191268 | c.1228-279T>G | NM_004586.2 | |
| RPS6KA3 | ChrX:20213274 | c.326-11A>G | NM_004586.2 | |
| SLC26A4 | Chr7:107301201 | c.-103T>C | NM_000441.1 | rs60284988 |
| SLC26A4 | Chr7:107301244 | c.-60A>G | NM_000441.1 | rs545973091 |
| SLC26A4 | Chr7:107301301 | c.-4+1G>C | NM_000441.1 | |
| SLC26A4 | Chr7:107301305 | c.-4+5G>A | NM_000441.1 | rs727503425 |
| SLC26A4 | Chr7:107323842 | c.918+45_918+47delCAA | NM_000441.1 | |
| SLC26A4 | Chr7:107330533 | c.1150-35_1150-28delTTTGTAGG | NM_000441.1 | |
| SLC26A4 | Chr7:107334836 | c.1264-12T>A | NM_000441.1 | |
| SLC26A4 | Chr7:107336364 | c.1438-7dupT | NM_000441.1 | rs754734032 |
| SLC26A4 | Chr7:107341513 | c.1708-27_1708-11delTAAGTAACTTGACATTT | NM_000441.1 | |
| SLC26A4 | Chr7:107350439 | c.2090-52_2090-49delCAAA | NM_000441.1 | |
| SLC29A3 | Chr10:73122778 | c.*413G>A | NM_018344.5 | |
| SLC52A2 | Chr8:145582843 | c.-110-1G>A | NM_024531.4 | |
| SNAI2 | Chr8:49833972 | c.-149_-148delCGinsTA | NM_003068.4 | |
| SOX10 | Chr22:38379877 | c.-84-2A>T | NM_006941.3 | |
| SOX10 | Chr22:38412215 | c.-31954C>T | NM_006941.3 | rs606231342 |
| SOX10 | Chr22:38412781 | c.-32520C>G | NM_006941.3 | rs533778281 |
| TIMM8A | ChrX:100601671 | c.133-23A>C | NM_004085.3 | rs869320666 |
| TMC1 | Chr9:75315577 | c.362+18A>G | NM_138691.2 | |
| TYR | Chr11:88960973 | c.1037-18T>G | NM_000372.4 | |
| USH2A | Chr1:215821092 | c.14583-20C>G | NM_206933.2 | |
| USH2A | Chr1:215967783 | c.9959-4159A>G | NM_206933.2 | |
| USH2A | Chr1:216039721 | c.8845+628C>T | NM_206933.2 | |
| USH2A | Chr1:216064540 | c.7595-2144A>G | NM_206933.2 | rs786200928 |
| USH2A | Chr1:216247476 | c.5573-834A>G | NM_206933.2 | |
| USH2A | Chr1:216592035 | c.486-14G>A | NM_206933.2 | rs374536346 |
| USH2A | Chr1:216596610 | c.-259G>T | NM_206933.2 | |

| | | | |
|---|---|---|---|
| WFS1 | Chr4:6271704 | c.-43G>T | NM_006005.3 |

## Test Strengths

Our panel assay enables the detection of common deletions in GJB6 such as ((~309 kb del (GJB6-D13S1830) and ~232 kb del (GJB6-D13S1854)).

**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

Variants in the *KCNE1* gene should not be used for risk assessment at the moment. Specifically, *KCNE1* c.253G>A, p.(Asp85Asn) variant has been considered to be a mild risk factor for acquired long QT syndrome. However, in the newest version of the reference genome GRCh38, a gene *KCNE1B*, nearly identical to *KCNE1* has appeared. By using standard NGS technologies, as well as Sanger sequencing, it is not possible to get reliable region-specific sequences for these genes. It is likely that reads that have been earlier mapped to *KCNE1* actually belong to *KCNE1B*. Moreover, it is currently unclear whether *KCNE1B* produces a protein product, and if a protein is produced, whether the gene is expressed in heart. More independent data characterizing *KCNE1B* and its function are needed. Currently, all *KCNE1* sequence data and the literature related to *KCNE1* variants should be interpreted with caution.

The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *OTOA* (NM_144672:22-27), *PDZD7* (NM_024895:10), *POLR1C* (NM_001318876:9), *STRC* (NM_153700:1-18). Note that we are able to detect variant in exons 19-29 of STRC, but our abilities are limited due to the high degree of homology that is shared between these exons and other regions of the genome. Whole gene deletions of STRC can and have been detected.

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 Blueprint Genetics comprehensive hearing loss and deafness panel covers classical genes associated with Waardenburg syndrome, Alport syndrome, sensorineural hearing loss, unilateral and bilateral, non-syndromic genetic deafness, Pendred syndrome, Usher syndrome, Stickler syndrome, Jervell and Lange-Nielsen syndrome, Mohr-Tranebjaerg syndrome, Norrie disease, Treacher Collins syndrome, CHARGE syndrome and Branchio-oto-renal (BOR) syndrome. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

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).

| | 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.

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## ICD codes

Commonly used ICD-10 codes when ordering the Comprehensive Hearing Loss and Deafness Panel

| ICD-10 | Disease |
|---|---|

| | |
|---|---|
| E70.30 | Waardenburg syndrome |
| Q87.89 | Alport syndrome |
| F84.2 | Rett syndrome |
| H90.5 | Sensorineural hearing loss, unilateral and bilateral |
| E07.1 | Pendred syndrome |
| H35.50 | Usher syndrome, type IV |
| Q89.8 | Stickler syndrome |
| G31.89 | Mohr-Tranebjaerg syndrome |
| H35.50 | Norrie disease |
| Q75.4 | Treacher Collins syndrome |
| Q89.8 | CHARGE syndrome |
| H49.40 | Progressive external ophthalmoplegia |
| Q87.89 | Branchio-oto-renal (BOR) syndrome |
| G11.9 | Hereditary ataxia |
| C94.2 | Acute Megakaryoblastic Leukemia |
| K59.8 | Chronic Intestinal Pseudoobstruction |
| T36.5 | Adverse effect of aminoglycosides |
| G93.41 | Metabolic Encephalopathy |
| H49.81 | Kearns Sayre Syndrome |
| E88.42 | MERFF Syndrome |
| H47.013 | Nonarteritic Anterior Ischemic Optic Neuropathy |
| G60.2 | Neuropathy in association with hereditary ataxia |
| G30 | Alzheimer's Disease |
| G25.5 | Chorea |
| G40 | Epilepsy and recurrent seizures |
| I42 | Cardiomyopathy |
| N26.9 | Focal Segmental Glomerulosclerosis |
| G31.82 | Leigh's Disease |
| H47.2 | Leber's hereditary optic neuropathy |
| G71.3 | Mitochondrial Myopathy |
| I42.1 | Hypertrophic Cardiomyopathy |

| | |
|---|---|
| E11.9 | Non-Insulin Dependent Diabetes Mellitus |
| Z86.74 | Personal history of sudden cardiac arrest |
| H90.3 | Sensorineural Hearing Loss |

## Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

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

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

## Resources

- Alford RL et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis ofhearingloss. Genet Med. 2014 Apr;16(4):347-55.
- Alport Syndrome Foundation
- American Hearing Research Foundation
- American Society for Deaf Children
- British Deaf Association
- CHARGE Syndrome Foundation
- GeneReviews - BOR Syndrome
- GeneReviews - Deafness and Hereditary Hearing Loss
- GeneReviews - Pendred Syndrome
- GeneReviews - Stickler Syndrome
- GeneReviews - Treacher Collins syndrome
- GeneReviews - Usher Syndrome, type I
- GeneReviews - Usher Syndrome, type II
- GeneReviews - Waardenburg Syndrome
- Hearing Health Foundation
- Hearing Link
- Hereditary Hearing loss
- NORD - Alport Syndrome
- NORD - BOR Syndrome
- NORD - CHARGE Syndrome
- NORD - Jervell and Lange-Nielsen Syndrome
- NORD - Norrie Disease
- NORD - Stickler Syndrome
- NORD - Treacher Collins syndrome
- NORD - Usher Syndrome
- NORD - Waardenburg Syndrome
- National Association of the Deaf US
- Norrie Disease Association
- Sloan-Heggen CM et al. Navigating genetic diagnostics in patients with hearing loss. Curr Opin Pediatr. 2016 Dec;28(6):705-712.
- Stickler Syndrome Support Group UK
- Stickler Syndrome Support Group US
- The Cain Foundation for BOR syndrome
- Usher Syndrome Coalition