Blueprint Genetics

Primary Immunodeficiency (PID) and Primary Ciliary Dyskinesia (PCD) Panel

Test code: IM0801

Panel is ideal for patients with a clinical suspicion of primary immunodeficiency (PID), especially, if primary ciliary dyskinesia (PCD) is considered important for differential diagnostics.

About Primary Immunodeficiency (PID) and Primary Ciliary Dyskinesia (PCD)

Primary immunodeficiencies (PIDs) are a genetically heterogeneous group of diseases. The International Union of Immunological Societies Expert Committee categorizes PIDs into nine different categories: 1) combined immunodeficiencies, 2) combined immunodeficiencies with associated or syndromic features, 3) predominantly antibody deficiencies, 4) diseases of immune dysregulation, 5) congenital defects of phagocyte number, function, or both, 6) defects in intrinsic and innate immunity, 7) autoinflammatory disorders, 8) complement deficiencies and 9) phenocopies of PIDs. Despite a heterogeneous genetic basis, the core symptoms are often very similar and can complicate the diagnosis. In addition, many PIDs may be included in more than one category. Without knowing the specific mutation in the causative gene, treatment choice can be a complicated process. Also, type and site of and specific organisms causing the infections may help to classify the disease. In addition to immune-related symptoms, many PIDs have non-immune manifestations. The prevalence of individual PIDs have a wide range, but the combined prevalence of all primary immunodeficiencies is reported to be as high as 5-8:10,000. Some recently identified PIDs are extremely rare.

Primary ciliary dyskinesia (PCD) is a disorder characterized by chronic respiratory tract infections, situs abnormalities (situs ambiguous and situs inversus), and sometimes infertility due to abnormal sperm motility. The signs and symptoms of this condition are caused by abnormal cilia. Affected patients may have signs of PCD at birth or within the first few months of life; however, the symptoms and disease onset vary depending on the underlying genetic defect. Most full-term neonates have respiratory distress with tachypnea (infant acute respiratory distress syndrome). Typical findings in infants and children include daily rhinitis and daily year-round wet cough occurring soon after birth with associated recurrent or chronic infections of the lower airways. Patients with PCD, especially young children, may also experience recurrent ear infections (otitis media). The prevalence of PCD is difficult to determine. Among population isolates with a high rate of consanguinity, the incidence rate may be especially high. The total number of individuals with PCD in the United States is estimated to be 12,000-17,000. PCD has an estimated incidence of 1:15,000-1:30,000 live births; however, this is probably an underestimate. The Primary Ciliary Dyskinesia Panel includes testing for cystic fibrosis (CF), which is characterized by the production of sweat with a high salt content and mucus secretions with an abnormal viscosity. CF is caused by mutations in the *CFTR* gene. The disease is chronic and generally progressive, with onset usually occurring during early childhood.

Availability

3-4 weeks

Gene set description

Genes in the Primary Immunodeficiency (PID) and Primary Ciliary Dyskinesia (PCD) Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ACD	Dyskeratosis congenita, autosomal dominant 6, Dyskeratosis congenita, autosomal recessive 7	AD/AR	2	8
ACP5	Spondyloenchondrodysplasia with immune dysregulation	AR	12	26
ACTB*	Baraitser-Winter syndrome	AD	55	60

ADA	Severe combined immunodeficiency due to adenosine deaminase deficiency	AR	49	93
ADAM17	Inflammatory skin and bowel disease, neonatal 1	AR	1	7
ADAR	Dyschromatosis symmetrica hereditaria, Aicardi-Goutières syndrome	AD/AR	25	226
AICDA	Immunodeficiency with hyper-IgM	AD/AR	14	50
AIRE	Autoimmune polyendocrinopathy syndrome	AD/AR	73	134
AK2	Reticular dysgenesis	AR	14	17
ALPI	Inflammatory bowel disease	AR		5
AP3B1	Hermansky-Pudlak syndrome	AR	14	34
ARHGEF1	Idiopathic bronchiectasis, Immunodeficiencies with antibody defects	AR		1
ARMC4*	Ciliary dyskinesia	AR	18	17
ARPC1B	Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease	AR	2	4
ATM	Breast cancer, Ataxia-Telangiectasia	AD/AR	1047	1109
ATP6AP1	Immunodeficiency 47	XL	5	5
BACH2	BACH2-related immunodeficiency and autoimmunity (BRIDA)	AD		2
BCL10	Immunodeficiency 37	AR	16	1
BCL11B	Immunodeficiency 49	AD	8	12
BLM	Bloom syndrome	AR	152	119
BLNK	Agammaglobulinemia 4	AR	2	3
BTK	Hypogammaglobulinemia, Agammaglobulinemia and isolated hormone deficiency, Agammaglobulinemia	XL	114	908
C11ORF70	Primary ciliary dyskinesia	AR		5
C17ORF62	Chronic granulomatous disease	AR		1
C1QA	C1q deficiency	AR	2	7
C1QB	C1q deficiency	AR	4	8
C1QC	C1q deficiency	AR	4	10
C1S	Complement component C1s deficiency	AR	4	10
C2*	Complement component 2 deficiency	AR	4	9
C21ORF59	Ciliary dyskinesia	AR	5	4
C3	Hemolytic uremic syndrome, atypical, Complement component 3 deficiency, Macular degeneration, age-related	AD/AR	6	87
CARD11	B-cell expansion with NFKB and T-cell anergy, Immunodeficiency	AD/AR	12	9

CARD14	Psoriasis	AD	9	29
CARD9	Candidiasis, familial, 2	AR	8	25
CASP10	Autoimmune lymphoproliferative syndrome	AD	5	7
CASP8	Caspase 8 defiency	AR	2	7
CCDC103	Ciliary dyskinesia	AR	4	5
CCDC114	Ciliary dyskinesia	AR	9	8
CCDC39	Ciliary dyskinesia	AR	39	47
CCDC40	Ciliary dyskinesia	AR	33	43
CCDC65	Ciliary dyskinesia	AR	2	2
CCNO	Ciliary dyskinesia	AR	11	10
CD19	Immunodeficiency, common variable	AR	8	9
CD247	Immunodeficiency	AR	8	4
CD27	Lymphoproliferative syndrome	AR	4	8
CD3D	Immunodeficiency	AR	3	5
CD3E	Immunodeficiency	AR	4	7
CD3G	Immunodeficiency	AR	5	3
CD40	Immunodeficiency with Hyper-IgM	AR	5	10
CD40LG	Immunodeficiency, with hyper-IgM	XL	35	231
CD46*	Hemolytic uremic syndrome, atypical	AD/AR	5	81
CD55	Blood group, Cromer system	BG	7	7
CD59	CD59 deficiency	AR	4	8
CD70	Primary immunodeficiency	AR		4
CD79A	Agammaglobulinemia 3	AR	3	7
CD79B	Agammaglobulinemia 6	AR	2	3
CD81	Immunodeficiency, common variable, 6	AR	1	1
CD8A	CD8 deficiency	AR	1	1
CDCA7	Immunodeficiency-centromeric instability-facial anomalies syndrome 3	AR	4	6
CDK9		AR		1
CEBPE	Specific granule deficiency 1	AR	3	4
CECR1	Polyarteritis nodosa, ADA2 deficiency	AR	15	50
CENPF	Ciliary dyskinesia -Lethal Ciliopathy	AR	13	8

CFB	Complement factor B deficiency, Hemolytic uremic syndrome, atypical	AD/AR	2	26
CFD	Complement factor D deficiency	AR	2	3
CFH*	Hemolytic uremic syndrome, atypical, Complement factor H deficiency, Basal laminar drusen	AD/AR	18	305
CFI	Hemolytic uremic syndrome, atypical, Complement factor I deficiency	AD/AR	10	143
CFP	Properdin deficiency	XL	5	17
CFTR	Cystic fibrosis, Congenital bilateral absence of the vas deferens	AD/AR	518	1803
CHD7	Isolated gonadotropin-releasing hormone deficiency, CHARGE syndrome	AD	276	860
CIITA	Bare lymphocyte syndrome	AR	9	15
CLCN7	Osteopetrosis	AD/AR	15	98
CLPB	3-methylglutaconic aciduria with cataracts, neurologic involvement, and neutropenia (MEGCANN)	AR	26	25
COLEC11	3MC syndrome	AR	6	13
COPA	Autoimmune interstitial lung, joint, and kidney disease	AD	6	6
CORO1A*	Immunodeficiency	AR	41	6
CR2	Common variable immunodeficiency	AR	2	16
CSF2RA*	Surfactant metabolism dysfunction, pulmonary	XL	2	17
CSF2RB	Surfactant metabolism dysfunction, pulmonary, 5	AR	2	6
CSF3R	Neutrophilia, hereditary	AD	13	13
CTC1	Cerebroretinal microangiopathy with calcifications and cysts	AR	21	33
CTLA4	Autoimmune lymphoproliferative syndrome, type V	AD	11	34
CTPS1	Immunodeficiency 24	AR	1	1
CTSC	Periodontitis, juvenile, Haim-Munk syndrome, Papillon-Lefevre syndrome	AR	19	92
CXCR4	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome	AD	5	15
CYBA	Chronic granulomatous disease	AR	13	71
CYBB	Chronic granulomatous disease, Immunodeficiency	XL	69	780
DBR1	Immunodeficiency	AR		1
DCLRE1C*	Omenn syndrome, Severe combined immunodeficiency with sensitivity to ionizing radiation	AR	18	89
DDX58	Singleton-Merten syndrome	AD	4	3
DGKE	Nephrotic syndrome	AR	17	38
DKC1	Hoyeraal-Hreidarsson syndrome, Dyskeratosis congenita	XL	48	74

DNAAF1	Ciliary dyskinesia	AR	19	38
DNAAF2	Ciliary dyskinesia	AR	13	6
DNAAF3	Primary ciliary dyskinesia	AD/AR	11	5
DNAAF5	Ciliary dyskinesia	AR	9	5
DNAH1	Spermatogenic failure 18	AR	15	32
DNAH11*	Ciliary dyskinesia	AR	66	130
DNAH5	Ciliary dyskinesia	AR	140	197
DNAH9	Primary ciliary dyskinesia	AR		6
DNAI1	Ciliary dyskinesia	AR	17	35
DNAI2	Ciliary dyskinesia	AR	19	6
DNAJC21	Bone marrow failure syndrome 3	AR	5	11
DNAL1	Ciliary dyskinesia	AR	3	1
DNASE2	Primary immunodeficiency			2
DNMT3B	Immunodeficiency-centromeric instability-facial anomalies syndrome	AR	14	47
DOCK2	Immunodeficiency	AR	7	6
DOCK8	Hyper-IgE recurrent infection syndrome, Mental retardation, autosomal dominant 2	AR	54	168
DRC1	Primary ciliary dyskinesia	AD/AR	5	3
DYX1C1	Ciliary dyskinesia	AR	15	12
EFL1	Shwachman-Diamond syndrome		3	2
ELANE	Neutropenia	AD	43	217
EPG5	Vici syndrome	AR	36	66
ERCC6L2	Bone marrow failure syndrome 2	AR	4	9
EXTL3	Immunoskeletal dysplasia with neurodevelopmental abnormalities (ISDNA)	AR	4	8
FADD	Infections, recurrent, with encephalopathy, hepatic dysfunction, and cardiovascular malformations	AR	2	1
FAS	Autoimmune lymphoproliferative syndrome	AD/AR	31	133
FASLG	Autoimmune lymphoproliferative syndrome, type IB	AD	2	10
FCHO1	Common variable immunodeficiency	AR		
FERMT3	Leukocyte adhesion deficiency	AR	8	14
FOXN1	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	AR	6	6

FOXP3	Immunodysregulation, polyendocrinopathy, and enteropathy	XL	28	93
G6PC3	Neutropenia, severe congenital, Dursun syndrome	AR	11	37
G6PD	Glucose-6-phosphate dehydrogenase deficiency	XL	45	226
GAS2L2	Primary ciliary dyskinesia	AR		3
GAS8	Ciliary dyskinesia, primary, 33	AR	4	6
GATA2	Myelodysplastic syndrome, Chronic neutropenia associated with monocytopenia, evolving to myelodysplasia and acute myeloid leukemia, Acute myeloid leukemia, Emberger syndrome, Immunodeficiency	AD	30	142
GFI1	Neutropenia, severe congenital, 2 autosomal dominant, Neutropenia, nonimmune chronic idiopathic, of adults	AD	2	6
GINS1	Immunodeficiency	AR	4	4
HAX1	Neutropenia, severe congenital	AR	11	21
HELLS	Immunodeficiency-centromeric instability-facial anomalies syndrome 4	AR	6	6
HYDIN*,#	Primary ciliary dyskinesia	AD/AR	5	25
HYOU1	Combined immunodeficiency	AR		2
ICOS	Immunodeficiency, common variable, 1	AR	3	4
IFIH1	Singleton-Merten syndrome, Aicardi-Goutieres syndrome 7	AD/AR	14	19
IFNAR2	Immunodeficiency 45	AR	1	2
IFNGR1	Immunodeficiency	AD/AR	16	42
IFNGR2	Immunodeficiency	AR	4	18
IGLL1*	Agammaglobulinemia	AR	2	3
IKBKB	Immunodeficiency 15	AR	2	7
IKZF1#	Immunodeficiency, common variable, 13	AD	10	35
IL10	Graft vs. host disease	AD	1	5
IL10RA	Inflammatory bowel disease	AR	4	43
IL10RB	Inflammatory bowel disease	AR	2	19
IL12B	Immunodeficiency 28, Immunodeficiency 29	AR	4	13
IL12RB1	Immunodeficiency	AR	13	82
IL17RA	Immunodeficiency 51	AR	8	17
IL17RC	Candiasis, familial, 9	AR	3	4
IL1RN	Osteomyelitis, sterile multifocal, with periostitis and pustulosis	AR	6	12
IL21	Immunodeficiency, common variable, 11	AR	1	1

IL21R	Immunodeficiency, primary, autosomal recessive, IL21R-related	AR	3	9
IL23R	Primary immunodeficiency	AR	1	
IL2RA	Interleukin 2 receptor, alpha, deficiency	AR	6	6
IL2RB	Primary immunodeficiency	AR		
IL2RG	Combined immunodeficiency	XL	54	243
IL36RN	Pustular psoriasis, generalized	AR	6	26
IL6ST	Primary immunodeficiency	AR		
IL7R	Severe combined immunodeficiency, , T-cell negative, B-cell positive, NK cell positive	AR	23	48
INVS	Nephronophthisis	AR	16	34
IRAK4	IRAK4 deficiency, Invasive pneumococcal disease, recurrent, isolated, 1	AR	12	29
IRF2BP2	Immunodeficiency, common variable, 14	AD	1	2
IRF8	Immunodeficiency 32A (CD11C-positive/CD1C-positive dendritic cell deficiency), Immunodeficiency 32B (monocyte and dendritic cell deficiency)	AD/AR	4	8
ISG15	Immunodeficiency, with basal ganglia calcification	AR	3	3
ITGB2	Leukocyte adhesion deficiency	AR	33	118
ITK	Lymphoproliferative syndrome	AR	4	11
JAGN1	Neutropenia, severe congenital	AR	8	8
JAK1	Primary immunodeficiency	AR	4	6
JAK3	Severe combined immunodeficiency, , T cell-negative, B cell-positive, natural killer cell-negative	AR	30	66
KRAS*	Noonan syndrome, Cardiofaciocutaneous syndrome	AD	63	35
LAMTOR2	Immunodeficiency due to defect in MAPBP-interacting protein	AR	1	1
LAT	Immunodeficiency 52	AR	2	18
LCK	Immunodeficiency	AR	2	3
LIG1	Primary immunodeficiency	AR		3
LIG4	Severe combined immunodeficiency with sensitivity to ionizing radiation, LIG4 syndrome	AR	18	36
LPIN2	Majeed syndrome	AR	12	14
LRBA	Common variable immunodeficiency	AR	23	64
LRRC6	Ciliary dyskinesia	AR	10	19
LYST*	Chediak-Higashi syndrome	AR	50	97

MAGT1	Immunodeficiency, with magnesium defect, Epstein-Barr virus infection and neoplasia, Mental retardation, X-linked 95	XL	8	14
MALT1	Immunodeficiency	AR	3	5
MAP3K14	Primary immunodeficiency with multifaceted aberrant lymphoid immunity	AR	1	2
MASP1	3MC syndrome	AR	11	22
MCIDAS	Primary ciliary dyskinesia	AR	4	3
MEFV	Familial Mediterranean fever	AD/AR	29	182
MKL1	Primary immunodeficiency	AR		4
MOGS	Congenital disorder of glycosylation	AR	7	8
MRE11A	Ataxia-telangiectasia-like disorder-1	AR	57	56
MSN*	Immunodeficiency 50	XL	2	2
MTHFD1	Severe combined immunodeficiency	AR	9	11
MVK	Mevalonic aciduria, Hyper-IgD syndrome, Porokeratosis 3, multiple types	AD/AR	35	181
MYD88	MYD88 deficiency	AR	5	5
MYO5A	Griscelli syndrome	AR	7	9
NBN	Breast cancer, Nijmegen breakage syndrome	AD/AR	188	97
NCF1*,#	Chronic granulomatous disease	AR	18	44
NCF2	Chronic granulomatous disease	AR	19	72
NCF4	Granulomatous disease	AR	4	5
NCSTN	Acne inversa, familial 1	AD	7	30
NFKB1	Common variable immunodeficiency	AD	8	17
NFKB2	Common variable immunodeficiency	AD	6	11
NFKBIA	Ectodermal dysplasia, anhidrotic, with T-cell immunodeficiency	AD	5	11
NHEJ1	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	AR	15	16
NHP2	Dyskeratosis congenita	AR	5	3
NLRC4	Autoinflammation with infantile enterocolitis (AIFEC), Familial cold autoinflammatory syndrome 4	AD	6	8
NLRP1	Palmoplantar carcinoma, multiple self-healing, Autoinflammation with arthritis and dyskeratosis	AD/AR	5	15
NLRP12	Familial cold autoinflammatory syndrome	AD	12	12
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

NME8	Ciliary dyskinesia	AR	1	6
NOD2	Blau syndrome, Sarcoidosis, early-onset	AD/AR	12	70
NOP10	Dyskeratosis congenita	AR	1	1
NRAS	Noonan syndrome	AD	31	14
NSMCE3	Lung disease, immunodeficiency, and chromosome breakage syndrome (LICS)	AR	2	2
OFD1	Simpson-Golabi-Behmel syndrome, Retinitis pigmentosa, Orofaciodigital syndrome, Joubert syndrome	XL	153	160
ORAI1	Immunodeficiency, Myopathy, tubular aggregate, 2	AR	9	13
OTULIN	Autoinflammation, panniculitis, and dermatosis syndrome (AIPDS)	AR	8	3
PARN*	Pulmonary fibrosis and/or bone marrow failure, Dyskeratosis congenita	AD/AR	15	29
PEPD	Prolidase deficiency	AR	12	31
PGM3	Immunodeficiency 23	AR	14	15
PIGA*	Multiple congenital anomalies-hypotonia-seizures syndrome	XL	24	27
PIH1D3#	Ciliary dyskinesia, primary, 36	XL	2	12
PIK3CD*	Immunodeficiency	AD	6	12
PIK3R1	Agammaglobulinemia, SHORT syndrome	AD/AR	33	24
PLCG2	Familial cold autoinflammatory syndrome 3 (PLAID), Autoinflammation, antibody deficiency, and immune dysregulation syndrome (APLAID)	AD	7	13
PMS2*	Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	319	342
PNP	Purine nucleoside phosphorylase deficiency	AR	11	33
POLD1	Colorectal cancer, Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome, Idiopathic bronchiectasis, Immunodeficiency	AD/AR	3	31
POLE	Colorectal cancer, Facial dysmorphism, immunodeficiency, livedo, and short stature syndrome (FILS syndrome)	AD/AR	8	70
POLE2	Combined immunodeficiency	AR		3
POMP	Keratosis linearis with ichthyosis congenita and sclerosing keratoderma	AR	5	4
PRF1	Lymphoma, non-Hodgkin, Aplastic anemia, adult-onset, Hemophagocytic lymphohistiocytosis	AR	24	183
PRG4	Camptodactyly-arthropathy-coxa vara-pericarditis syndrome	AR	6	35
PRKCD	Autoimmune lymphoproliferative syndrome type III	AR	4	6
PRKDC	Immunodeficiency	AR	6	9
PSENEN	Acne inversa, familial, 2	AD	7	17

PSMB8	Nakajo-Nishimura syndrome, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, Autoinflammation, lipodystrophy, and dermatosis syndrome, Joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome	AR	5	9
PSTPIP1	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne	AD	5	29
PTPRC	Severe combined immunodeficiency, , T-cell negative, B-cell positive, NK cell positive	AR	4	5
RAB27A	Griscelli syndrome, Elejalde syndrome	AR	18	54
RAC2	Neutrophil immunodeficiency syndrome	AD	2	3
RAG1	Omenn syndrome, Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity, T cell-negative, B cell-negative, natural killer cell-positive severe combined immunodeficiency, Combined cellular and humoral immune defects with granulomas	AR	47	184
RAG2	Omenn syndrome, Combined cellular and humoral immune defects with granulomas	AR	28	79
RASGRP1	Primary immunodeficiency	AR	1	3
RBCK1	Polyglucosan body myopathy	AR	11	14
RECQL4	Baller-Gerold syndrome, RAPADILINO syndrome, Rothmund-Thomson syndrome	AR	82	114
RELA	Autoimmune lymphoproliferative syndrome	AD	1	3
RFX5	Bare lymphocyte syndrome	AR	4	10
RFXANK	MHC class II deficiency	AR	8	16
RFXAP	Bare lymphocyte syndrome	AR	6	9
RHOH	T-cell immunodeficiency with epidermodysplasia verruciformis	AD/AR		1
RIPK1	Primary immunodeficiency	AR	3	1
RLTPR	Combined immunodeficiency	AR	11	8
RMRP	Cartilage-hair hypoplasia, Metaphyseal dysplasia without hypotrichosis, Anauxetic dysplasia	AR	87	123
RNASEH2A	Aicardi-Goutières syndrome	AR	13	21
RNASEH2B	Aicardi-Goutières syndrome	AR	16	41
RNASEH2C	Aicardi-Goutières syndrome	AR	6	14
RNF168	RIDDLE syndrome	AR	4	5
RNF31	HOIP and LUBAC deficiency	AR		1
RNU4ATAC	Roifman syndrome, Microcephalic osteodysplastic primordial dwarfism type 1, Microcephalic osteodysplastic primordial dwarfism type 3	AR	15	24

RORC	Immunodeficiency 42	AR	3	3
RPGR	Retinitis pigmentosa, Cone-rod dystrophy, X-linked, 1, Macular degeneration, X-linked atrophic, Retinitis pigmentosa 3	XL	79	218
RPSA	Asplenia, isolated congenital	AD	7	8
RSPH1	Ciliary dyskinesia	AR	14	10
RSPH3	Ciliary dyskinesia, primary, 32	AR	7	5
RSPH4A	Ciliary dyskinesia	AR	18	24
RSPH9	Ciliary dyskinesia	AR	8	12
RTEL1	Pulmonary fibrosis and/or bone marrow failure, Dyskeratosis congenita	AD/AR	58	51
SAMD9	Mirage syndrome, Tumoral calcinosis, normophosphatemic	AD/AR	10	27
SAMD9L	Ataxia-pancytopenia syndrome	AD	4	16
SAMHD1	Aicardi-Goutières syndrome, Chilblain lupus 2	AD/AR	25	56
SBDS*	Aplastic anemia, Shwachman-Diamond syndrome, Severe spondylometaphyseal dysplasia	AD/AR	19	90
SERPING1	Angioedema, Complement component 4, partial deficiency of	AD/AR	34	563
SH2D1A	Lymphoproliferative syndrome	XL	21	129
SLC29A3	Histiocytosis-lymphadenopathy plus syndrome, Dysosteosclerosis	AR	17	25
SLC35C1	Congenital disorder of glycosylation, Leukocyte adhesion deficiency	AR	6	7
SLC37A4	Glycogen storage disease	AR	49	113
SLC39A7	Agammaglobulinemia	AR		
SLC46A1	Folate malabsorption	AR	17	23
SLC7A7	Lysinuric protein intolerance	AR	55	67
SMARCAL1	Schimke immunoosseous dysplasia	AR	20	88
SMARCD2	Specific granule defiency 2	AR	3	1
SP110	Hepatic venoocclusive disease with immunodeficiency	AR	8	8
SPAG1	Primary ciliary dyskinesia	AR	18	11
SPINK5	Netherton syndrome	AR	29	85
SPPL2A	Primary immunodeficiency	AR	1	
SRP54	Shwachman-Diamond syndrome	AD	3	
SRP72*	Bone marrow failure syndrome 1	AD	2	5
STAT1	Immunodeficiency	AD/AR	39	122
STAT2	Immunodeficiency	AR	3	6

STAT3	Hyper-IgE recurrent infection syndrome, Autoimmune disease, multisystem, infantile onset	AD	47	152
STAT5B*	Growth hormone insensitivity with immunodeficiency	AR	9	13
STIM1	Stormorken syndrome, Immunodeficiency, Myopathy, tubular aggregate 1	AD/AR	13	24
STK36	Primary ciliary dyskinesia	AR		5
STK4	T-cell immunodeficiency syndrome, recurrent infections, autoimmunity,	AR	3	7
STX11	Hemophagocytic lymphohistiocytosis, familial	AR	8	22
STXBP2	Hemophagocytic lymphohistiocytosis, familial	AR	12	77
TAP1	Bare lymphocyte syndrome	AR	1	7
TAP2	Bare lymphocyte syndrome	AR	4	8
TAPBP	Bare lymphocyte syndrome	AR	1	2
TBX1	Conotruncal anomaly face syndrome	AD	17	72
TCF3	Agammaglobulinemia 8, autosomal dominant	AD	1	5
TCN2	Transcobalamin II deficiency	AR	9	35
TERC	Aplastic anemia, Pulmonary fibrosis and/or bone marrow failure, telomere-related, Dyskeratosis congenita	AD	42	73
TERT	Aplastic anemia, Pulmonary fibrosis and/or bone marrow failure, telomere-related, Dyskeratosis congenita	AD/AR	48	156
TFRC	Immunodeficiency 46	AR	8	2
TGFB1	Diaphyseal dysplasia Camurati-Engelmann	AD	15	23
THBD	Thrombophilia due to thrombomodulin defect, Hemolytic uremic syndrome, atypical	AD	5	28
TINF2	Revesz syndrome, Dyskeratosis congenita	AD	25	42
TMC6	Epidermodysplasia verruciformis	AR	8	7
TMC8	Epidermodysplasia verruciformis	AR	3	9
TMEM173	STING-associated vasculopathy, infantile-onsent (SAVI)	AD	4	10
TNFAIP3	Autoinflammatory syndrome, familial, Behcet-like	AD	8	23
TNFRSF13B	Common variable immunodeficiency, Immunoglobulin A deficiency	AD/AR	7	48
TNFRSF1A	Periodic fever (TNF receptor-associated periodic syndrome)	AD	19	106
TNFRSF4	Immunodeficiency	AR	1	1
TNFRSF9				
TRAF3IP2	Candidiasis, familial 8	AR	1	3

TREX1	Vasculopathy, retinal, with cerebral leukodystrophy, Chilblain lupus, Aicardi-Goutières syndrome	AD/AR	30	71
TRNT1	Retinitis pigmentosa and erythrocytic microcytosis, Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay	AR	13	26
TTC37	Trichohepatoenteric syndrome, Primary immunodeficiency	AR	12	64
TTC7A	Gastrointestinal defects and immunodeficiency syndrome	AR	21	46
TYK2	Immunodeficiency	AR	9	9
UNC119	Immunodeficiency, Cone-rod dystrophy 2	AR	1	5
UNC13D	Hemophagocytic lymphohistiocytosis, familial	AR	22	192
UNC93B1*	Herpes simplex encephalitis, susceptibility to, 1	AR		2
UNG	Immunodeficiency with hyper-IgM, type 5	AR	6	7
USB1	Poikiloderma with neutropenia	AR	24	22
USP18*	Pseudo-TORCH syndrome 2	AR	40	1
VPS13B	Cohen syndrome	AR	351	203
VPS45	Neutropenia, severe congenital, 5, autosomal recessive	AR	3	4
WAS	Neutropenia, severe congenital, Thrombocytopenia, Wiskott-Aldrich syndrome	XL	57	439
WDR1		AR		8
WIPF1	Wiskott-Aldrich syndrome 2	AR	2	3
WRAP53	Dyskeratosis congenita	AR	7	6
XIAP*	Lymphoproliferative syndrome	XL	14	96
ZAP70	Selective T-cell defect	AR	15	29
ZBTB24	Immunodeficiency-Centromeric Instability-Facial Anomalies 2	AR	7	17
ZMYND10	Ciliary dyskinesia	AR	8	16
ZNF341*		AR		5

*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
ADA	Chr20:43248503	c.1079-15T>A	NM_000022.2	rs387906268
ADA	Chr20:43249076	c.976-34G>A	NM_000022.2	
ATM	Chr11:108093770	c.-174A>G	NM_000051.3	
ATM	Chr11:108094508	c.-31+595G>A	NM_000051.3	
ATM	Chr11:108098321	c.-30-1G>T	NM_000051.3	rs869312754
ATM	Chr11:108138753	c.2639-384A>G	NM_000051.3	
ATM	Chr11:108141209	c.2839-579_2839-576delAAGT	NM_000051.3	
ATM	Chr11:108151710	c.3403-12T>A	NM_000051.3	rs201370733
ATM	Chr11:108158168	c.3994-159A>G	NM_000051.3	rs864622543
ATM	Chr11:108164028	c.4612-12A>G	NM_000051.3	
ATM	Chr11:108179837	c.5763-1050A>G	NM_000051.3	rs774925473
ATM	Chr11:108214779	c.8418+681A>G	NM_000051.3	rs748635985
BTK	ChrX:100609705	c.1567-23A>C/G	NM_000061.2	
BTK	ChrX:100609705	c.1567-23A>G	NM_000061.2	
BTK	ChrX:100609705	c.1567-23A>C	NM_000061.2	
BTK	ChrX:100612468	c.1177+28_1177+29insAGAAAAAAGGT	NM_000061.2	
BTK	ChrX:100613695	c.895-11C>A	NM_000061.2	
BTK	ChrX:100625094	c.310-28_310-27delGCinsTG	NM_000061.2	
BTK	ChrX:100629415	c.240+109C>A	NM_000061.2	
BTK	ChrX:100629416	c.240+108T>G	NM_000061.2	
BTK	ChrX:100629827	c.142-205A>G	NM_000061.2	
BTK	ChrX:100630121	c.141+11C>T	NM_000061.2	rs138411530
BTK	ChrX:100641044	c.-31+6T>G	NM_000061.2	
BTK	ChrX:100641045	c.-31+5G>A/C/T	NM_000061.2	
BTK	ChrX:100641045	c.-31+5G>A	NM_000061.2	
BTK	ChrX:100641045	c.-31+5G>T	NM_000061.2	rs1131691354
BTK	ChrX:100641045	c.-31+5G>C	NM_000061.2	
BTK	ChrX:100641049	c.-31+1G>A/C	NM_000061.2	
BTK	ChrX:100641049	c.-31+1G>A	NM_000061.2	
BTK	ChrX:100641049	c.-31+1G>C	NM_000061.2	
BTK	ChrX:100641050	c.-31G>A	NM_000061.2	

BTK	ChrX:100641212	c.-193A>G	NM_000061.2	
C1QB	Chr1:22985931	c.-17-2A>C	NM_000491.3	
CCDC39	Chr3:180365042	c.1363-11A>G	NM_181426.1	
CCDC39	Chr3:180367928	c.1167+1261A>G	NM_181426.1	rs577069249
CCDC39	Chr3:180367941	c.1167+1248A>G	NM_181426.1	
CD40LG	ChrX:135736498	c.289-32_289-25delAAAATGAC	NM_000074.2	
CD40LG	ChrX:135736517	c.289-15T>A	NM_000074.2	
CD40LG	ChrX:135737600	c.347-915A>T	NM_000074.2	
CD46	Chr1:207930564	c.286+27delT	NM_002389.4	rs771669828
CECR1	Chr22:17664763	c.1082-1113delA	NM_017424.2	
CFTR	Chr7:117119654	c.-495C>T	NM_000492.3	rs397507565
CFTR	Chr7:117119797		NM_000492.3	
CFTR	Chr7:117119900	c.-249G>C	NM_000492.3	
CFTR	Chr7:117119984	c.-165G>A	NM_000492.3	rs145483167
CFTR	Chr7:117120064	c.-85C>G	NM_000492.3	
CFTR	Chr7:117120115	c.-34C>T	NM_000492.3	rs756314710
CFTR	Chr7:117120325	c.53+124T>C	NM_000492.3	
CFTR	Chr7:117179040	c.870-1113_870-1110delGAAT	NM_000492.3	rs397508809
CFTR	Chr7:117182041	c.1117-26_1117-25delAT	NM_000492.3	rs397508159
CFTR	Chr7:117199500	c.1393-18G>A	NM_000492.3	rs397508199
CFTR	Chr7:117218381	c.1585-9412A>G	NM_000492.3	rs397508229
CFTR	Chr7:117227774	c.1585-19T>C	NM_000492.3	rs778457306
CFTR	Chr7:117227921	c.1679+34G>T	NM_000492.3	rs767901668
CFTR	Chr7:117229521	c.1680-886A>G	NM_000492.3	rs397508266
CFTR	Chr7:117229524	c.1680-883A>G	NM_000492.3	
CFTR	Chr7:117229530	c.1680-877G>T	NM_000492.3	rs397508261
CFTR	Chr7:117243855	c.2908+19G>C	NM_000492.3	rs370683572
CFTR	Chr7:117246713	c.2909-15T>G	NM_000492.3	rs397508455
CFTR	Chr7:117246840	c.2988+33G>T	NM_000492.3	
CFTR	Chr7:117251609	c.3140-26A>G	NM_000492.3	rs76151804
CFTR	Chr7:117251619	c.3140-16T>A	NM_000492.3	rs767232138
CFTR	Chr7:117251624	c.3140-11A>G	NM_000492.3	
CFTR	Chr7:117266272	c.3469-1304C>G	NM_000492.3	
CFTR	Chr7:117267864	c.3717+40A>G	NM_000492.3	rs397508595

CFTR	Chr7:117280015	c.3718-2477C>T	NM_000492.3	rs75039782
CFTR	Chr7:117282680	c.3873+33A>G	NM_000492.3	rs397508622
CFTR	Chr7:117288374	c.3874-4522A>G	NM_000492.3	
CFTR	Chr7:117308395	c.*1233T>A	NM_000492.3	
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	Chr8:61763039	c.5405-13G>A	NM_017780.3	rs1131690787
CLCN7	Chr16:1506057	c.916+57A>T	NM_001287.5	
CLCN7	Chr16:1507356	c.739-18G>A	NM_001287.5	rs371893553
CTSC	Chr11:88070895	c.-55C>A	NM_001814.4	rs766114323
CYBA	Chr16:88712620	c.288-15C>G	NM_000101.3	
CYBB	ChrX:37639262	c.-69A>C	NM_000397.3	
CYBB	ChrX:37639262		NM_000397.3	
CYBB	ChrX:37639264	c.-67T>C	NM_000397.3	
CYBB	ChrX:37639266	c.-65C>T	NM_000397.3	
CYBB	ChrX:37639267	c.-64C>T	NM_000397.3	
CYBB	ChrX:37641327	c.46-14_46-11delTTCTinsGAA	NM_000397.3	
CYBB	ChrX:37641330	c.46-11T>G	NM_000397.3	
CYBB	ChrX:37642713	c.142-28_142-12delACTCTGCTCCCTTTCCC	NM_000397.3	
CYBB	ChrX:37642731	c.142-12delCinsACCTCTTCTAG	NM_000397.3	
CYBB	ChrX:37654041	c.483+978G>T	NM_000397.3	
CYBB	ChrX:37656474	c.674+1080A>G	NM_000397.3	
CYBB	ChrX:37656731	c.674+1337T>G	NM_000397.3	
CYBB	ChrX:37657051	c.675-1157A>G	NM_000397.3	
CYBB	ChrX:37664248	c.1152-11T>G	NM_000397.3	
DGKE	Chr17:54925466	c.888+40A>G	NM_003647.2	
DKC1	ChrX:153991099	c.-142C>G	NM_001363.3	rs199422241
DKC1	ChrX:153991100	c.-141C>G	NM_001363.3	
DKC1	ChrX:153993704	c.85-15T>C	NM_001363.3	
DNMT3B	Chr20:31395557	c.2421-11G>A	NM_006892.3	rs547940069
DOCK8	Chr9:317025	c.742-18C>G	NM_203447.3	rs112373444
DOCK8	Chr9:317028	c.742-15T>G	NM_203447.3	rs111627162
DOCK8	Chr9:368196	c.1797+61A>C	NM_203447.3	rs786205596

FAS	Chr10:90770494	c.506-16A>G	NM_000043.4	
FASLG	Chr1:172628081	c.-261T>C	NM_000639.1	
FOXP3	ChrX:49106917	c.*878A>G	NM_014009.3	
FOXP3	ChrX:49106919	c.*876A>G	NM_014009.3	
FOXP3	ChrX:49121118	c.-23+5G>A	NM_014009.3	
FOXP3	ChrX:49121121	c.-23+2T>G	NM_014009.3	
FOXP3	ChrX:49121122	c.-23+1G>A	NM_014009.3	
FOXP3	ChrX:49121122	c.-23+1G>T	NM_014009.3	
GATA2	Chr3:128202131	c.1017+572C>T	NM_032638.4	
GATA2	Chr3:128202162	c.1017+513_1017+540delGGAGTTTCCTATCCGGACATCTGCAGCC	NM_032638.4	
GATA2	Chr3:128202171	c.1017+532T>A	NM_032638.4	
GINS1	Chr20:25388397	c.-60A>G	NM_021067.3	
GINS1	Chr20:25388409	c.-48C>G	NM_021067.3	
IL10RB	Chr21:34668714	c.*52C>T	NM_000628.4	
IL2RG	ChrX:70327277	c.*307_*308delAA	NM_000206.2	
IL2RG	ChrX:70327278	c.*308A>G	NM_000206.2	
IL2RG	ChrX:70330553	c.270-15A>G	NM_000206.2	
IL2RG	ChrX:70331494	c.-105C>T	NM_000206.2	
IL7R	Chr5:35867853	c.379+288G>A	NM_002185.3	
IRAK4	Chr12:44178047	c.1188+520A>G	NM_016123.3	
ITGB2	Chr21:46320404	c.742-14C>A	NM_000211.3	rs183204825
ITGB2	Chr21:46321660	c.500-12T>G	NM_000211.3	
JAK3	Chr19:17943239	c.2680+89G>A	NM_000215.3	
JAK3	Chr19:17946035	c.1915-11G>A	NM_000215.3	
LAMTOR2	Chr1:156028185	c.*23C>A	NM_014017.3	
MEFV	Chr16:3306599	c.-12C>G	NM_000243.2	rs104895148
MEFV	Chr16:3306969	c.-382C>G	NM_000243.2	
MVK	Chr12:110029032	c.769-7dupT	NM_000431.2	rs104895348
OFD1	ChrX:13768358	c.935+706A>G	NM_003611.2	rs730880283
OFD1	ChrX:13773245	c.1130-22_1130-19delAATT	NM_003611.2	rs312262865
OFD1	ChrX:13773249	c.1130-20_1130-16delTTGGT	NM_003611.2	
PARN	Chr16:14724045	c.-165+2C>T	NM_001134477.2	
PMS2	Chr7:6027263	c.1145-31_1145-13delCTGACCCTCTTCTCCGTCC	NM_000535.5	rs751973268
PMS2	Chr7:6048599	c.23+21_23+28delTCCGGTGT	NM_000535.5	

PNP	Chr14:20942914	c.286-18G>A	NM_000270.3	
POLE	Chr12:133249181	c.1686+32C>G	NM_006231.2	rs762985435
POMP	Chr13:29233225	c.-95delC	NM_015932.5	rs112368783
PSENEN	Chr19:36236501	c.-192_-190delAGA	NM_172341.2	rs554724520
RAG2	Chr11:36619652	c.-28G>C	NM_000536.3	
RFXANK	Chr19:19307761	c.188-11C>T	NM_003721.3	rs201545133
RMRP	Chr9:35658026		NR_003051.3	rs781730798
RMRP	Chr9:35658026		NR_003051.3	
RMRP	Chr9:35658026		NR_003051.3	
RMRP	Chr9:35658026		NR_003051.3	
RMRP	Chr9:35658027		NR_003051.3	
RMRP	Chr9:35658027		NR_003051.3	
RMRP	Chr9:35658027		NR_003051.3	
RMRP	Chr9:35658027		NR_003051.3	rs727502775
RMRP	Chr9:35658027		NR_003051.3	
RMRP	Chr9:35658028		NR_003051.3	
RMRP	Chr9:35658028		NR_003051.3	
RMRP	Chr9:35658029		NR_003051.3	
RMRP	Chr9:35658029		NR_003051.3	
RMRP	Chr9:35658032		NR_003051.3	
RNASEH2B	Chr13:51501530	c.65-13G>A	NM_024570.3	
RNASEH2B	Chr13:51519550	c.511-13G>A	NM_024570.3	
RPGR	ChrX:38128234		NM_000328.2	
RPGR	ChrX:38160137	c.1059+363G>A	NM_001034853.1	
RPSA	Chr3:39448260	c.-34+5G>C	NM_002295.4	
SERPING1	Chr11:57365055	c.-163C>T	NM_000062.2	
SERPING1	Chr11:57365057	c.-161A>G	NM_000062.2	
SERPING1	Chr11:57365118	c.-100C>G	NM_000062.2	rs578018379
SERPING1	Chr11:57365720	c.-22-2A>C/G	NM_000062.2	
SERPING1	Chr11:57365720	c.-22-2A>C	NM_000062.2	
SERPING1	Chr11:57365720	c.-22-2A>G	NM_000062.2	
SERPING1	Chr11:57365721	c.-22-1G>A	NM_000062.2	
SERPING1	Chr11:57373471	c.686-12A>G	NM_000062.2	
SERPING1	Chr11:57373867	c.890-14C>G	NM_000062.2	

SERPING1	Chr11:57381788	c.1250-13G>A	NM_000062.2	
SH2D1A	ChrX:123499593	c.138-17_138-11delAGTTTAT	NM_002351.4	
SLC29A3	Chr10:73122778	c.*413G>A	NM_018344.5	
SPINK5	Chr5:147465956	c.283-12T>A	NM_006846.3	
SPINK5	Chr5:147484503	c.1431-12G>A	NM_006846.3	rs368134354
SPINK5	Chr5:147491511	c.1820+53G>A	NM_006846.3	rs754599628
STX11	Chr6:144508713	c.*85_*86insT	NM_003764.3	
STXBP2	Chr19:7705761	c.326-23_326-16delGCCCCACT	NM_006949.3	
TBX1	Chr22:19743578	c.-777C>T	NM_080647.1	
TBX1	Chr22:19743735	c.-620A>C	NM_080647.1	rs536892777
TCN2	Chr22:31011112	c.581-176A>T	NM_000355.3	
TERC	Chr3:169482870	n.-22C>T	NR_001566.1	
TERC	Chr3:169482906		NR_001566.1	
TERC	Chr3:169482948	n.-100C>G	NR_001566.1	rs199422256
TERC	Chr3:169483086		NR_001566.1	rs199422255
TERT	Chr5:1271334	c.2383-15C>T	NM_198253.2	rs574645600
TERT	Chr5:1295161	c.-57A>C	NM_198253.2	
THBD	Chr20:23030319		NM_000361.2	
THBD	Chr20:23030443	c.-302C>A	NM_000361.2	
TRNT1	Chr3:3188088	c.609-26T>C	NM_182916.2	
UNC13D	Chr17:73826245	c.2831-13G>A	NM_199242.2	
UNC13D	Chr17:73827442	c.2448-13G>A	NM_199242.2	rs753762300
UNC13D	Chr17:73839907	c.118-307G>A	NM_199242.2	
UNC13D	Chr17:73839908	c.118-308C>T	NM_199242.2	
WAS	ChrX:48547690	c.1339-19_1339-11delTGATCCCTGinsATCTGCAGACC	NM_000377.2	
ZAP70	Chr2:98349927	c.838-80G>A	NM_001079.3	rs113994173
ZAP70	Chr2:98354447	c.1624-11G>A	NM_001079.3	rs730880318

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level

- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *ARMC4* (NM_018076:9;NM_001290021:13), *CD55* (NM_001114752:10;NM_001300903:10), *CORO1A* (NM_007074:11), *CSF2RA* (NM_001161530:9), *HYDIN* (NM_001270974:6,8,12,18,20,21,23,26,27,31,35,37,45,47,50,52,57,58,64,70,75,78,82,83), *IL12RB1* (NM_153701:10), *NCF1* (NM_000265:1,5,8,9,11), *TNFRSF1A* (NM_001346092:6), *USP18* (NM_017414:11), *VPS45* (NM_001279353:13). 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

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.

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%
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.

		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=2084 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%)	92.9%(12/13)	99.98%
Heteroplasmic (<5%)	88.7% (47/53)	99.93%
Insertions and deletions by sequence analysis n=42 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)	>0.9999
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. 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 <20X sequencing depth 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 Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis is orthogonal confirmation. Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing when they do not meet our stringent NGS quality metrics for a true positive call. Reported heterozygous and homo/hemizygous copy number variations with a size <10 and <3 target exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen and confirmed 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, 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.

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ICD codes

Commonly used ICD-10 codes when ordering the Primary Immunodeficiency (PID) and Primary Ciliary Dyskinesia (PCD) Panel

ICD-10	Disease
Q34.8	Primary ciliary dyskinesia
Q34.8	Other specified congenital malformations of respiratory system
E84.0	Cystic fibrosis
N46.8	Male Infertility
Q89.3	Situs inversus
D80.9	Immunodeficiencies with antibody defects
D81.9	Combined immunodeficiencies

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

- Autoinflammatory Alliance
- Chronic Granulomatous Disease Association
- Cystic Fibrosis Foundation
- Cystic Fibrosis Research
- Cystic Fibrosis Trust
- Cystic Fibrosis Worldwide

- Dyskeratosis Congenita Outreach
- European Society for Immunodeficiencies
- GeneReviews - *CTFR*-Related Disorders
- GeneReviews - *ELANE*-Related Neutropenia
- GeneReviews - *WAS*-Related Disorders
- GeneReviews - Chronic Granulomatous Disease
- GeneReviews - Dyskeratosis Congenita
- GeneReviews - Familial Mediterranean Fever
- GeneReviews - Primary Ciliary Dyskinesia
- GeneReviews - X-Linked Severe Combined Immunodeficiency
- Immune Deficiency Foundation
- NORD - Chronic Granulomatous Disease
- NORD - Cyclic Neutropenia
- NORD - Cystic Fibrosis
- NORD - Dyskeratosis Congenita
- NORD - Familial Mediterranean Fever
- NORD - Muckle-Wells Syndrome
- NORD - Primary Ciliary Dyskinesia
- NORD - Severe Combined Immune Deficiency
- NORD - Wiskott-Aldrich Syndrome
- National Neutropenia Network
- Neutropenia Support Association
- PCD Family Support Group
- PCD Foundation
- Picard, C. et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018 Jan;38(1):96-128.
- Primary Immunodeficiency UK
- Shapiro J, et al. Diagnosis, Monitoring, and Treatment of Primary Ciliary Dyskinesia: PCD Foundation Consensus Recommendations Based on State of the Art Review. Pediatr Pulmonol. 2016 Feb;51(2):115-32.
- Strippoli MP, et al. Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. Eur Respir J. 2012 Jun;39(6):1482-91.
- Wiskott-Aldrich Foundation