Blueprint Genetics

Severe Combined Immunodeficiency Panel

Test code: IM0101

Is ideal for patients with a clinical suspicion of combined immunodeficiencies. The genes on this panel are included in the Primary Immunodeficiency Panel.

Approximately half of the cases with severe combined immunodeficiencies (SCIDs) are inherited in X-linked manner (*IL2RG*), while the inheritance is autosomal recessive for the other half. In addition to typical severe combined immunodeficiencies, this Panel has differential diagnostics power to several other combined immunodeficiencies generally less profound than SCIDs. This Panel is included in the comprehensive Primary Immunodeficiency Panel.

About Severe Combined Immunodeficiency

Severe combined immunedeficiencies (SCIDs) are a group of primary immunodeficiencies characterized by specific mutations in genes of T and B-lymphocyte systems and leading to little or no immune response. Different subtypes of SCIDs are characterized and subdivided by the presence of circulating T and B cells. T cells are absent or markedly decreased in the most types, but levels of B cells vary. In addition, both of these disease subgroups (T-B+ and T-B-) can occur with or without NK cells. Patients with SCID are susceptible to recurrent infections that can be fatal. The worldwide prevalence of SCID is estimated to be at least 1:100,000 births, while some genetically more homogenous populations may show markedly increased numbers. Mutations in *IL2RG* are the most common reason for SCIDs, explaining approximately 50% of all cases and close to 100% of X-linked cases.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Severe Combined Immunodeficiency Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ADA	Severe combined immunodeficiency due to adenosine deaminase deficiency	AR	49	93
AK2	Reticular dysgenesis	AR	14	17
ATM	Breast cancer, Ataxia-Telangiectasia	AD/AR	1047	1109
BCL11B	Immunodeficiency 49	AD	8	12
BLM	Bloom syndrome	AR	152	119
CARD11	B-cell expansion with NFKB and T-cell anergy, Immunodeficiency	AD/AR	12	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
CD8A	CD8 deficiency	AR	1	1
CIITA	Bare lymphocyte syndrome	AR	9	15
CORO1A*	Immunodeficiency	AR	41	6
DCLRE1C*	Omenn syndrome, Severe combined immunodeficiency with sensitivity to ionizing radiation	AR	18	89
DNMT3B	Immunodeficiency-centromeric instability-facial anomalies syndrome	AR	14	47
DOCK8	Hyper-IgE recurrent infection syndrome, Mental retardation, autosomal dominant 2	AR	54	168
EPG5	Vici syndrome	AR	36	66
FOXN1	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	AR	6	6
IFNGR1	Immunodeficiency	AD/AR	16	42
IKBKB	Immunodeficiency 15	AR	2	7
IL12RB1	Immunodeficiency	AR	13	82
IL2RA	Interleukin 2 receptor, alpha, deficiency	AR	6	6
IL2RG	Combined immunodeficiency	XL	54	243
IL7R	Severe combined immunodeficiency, , T-cell negative, B-cell positive, NK cell positive	AR	23	48
IRF8	Immunodeficiency 32A (CD11C-positive/CD1C-positive dendritic cell deficiency), Immunodeficiency 32B (monocyte and dendritic cell deficiency)	AD/AR	4	8
ITGB2	Leukocyte adhesion deficiency	AR	33	118
ITK	Lymphoproliferative syndrome	AR	4	11
JAK3	Severe combined immunodeficiency, , T cell-negative, B cell-positive, natural killer cell-negative	AR	30	66
LAT	Immunodeficiency 52	AR	2	18
LCK	Immunodeficiency	AR	2	3
LIG4	Severe combined immunodeficiency with sensitivity to ionizing radiation, LIG4 syndrome	AR	18	36
LRBA	Common variable immunodeficiency	AR	23	64
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

MSN*	Immunodeficiency 50	XL	2	2
NHEJ1	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	AR	15	16
NSMCE3	Lung disease, immunodeficiency, and chromosome breakage syndrome (LICS)	AR	2	2
ORAI1	Immunodeficiency, Myopathy, tubular aggregate, 2	AD/AR	9	13
PARN*	Pulmonary fibrosis and/or bone marrow failure, Dyskeratosis congenita	AD/AR	15	29
PGM3	Immunodeficiency 23	AR	14	15
PIK3CD*	Immunodeficiency	AD	6	12
PMS2*	Mismatch repair cancer syndrome, Colorectal cancer, hereditary nonpolyposis	AD/AR	319	342
PNP	Purine nucleoside phosphorylase deficiency	AR	11	33
POLE	Colorectal cancer, Facial dysmorphism, immunodeficiency, livedo, and short stature syndrome (FILS syndrome)	AD/AR	8	70
POLE2	Combined immunodeficiency	AR		3
PRKDC	Immunodeficiency	AR	6	9
PTPRC	Severe combined immunodeficiency, , T-cell negative, B-cell positive, NK cell positive	AR	4	5
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
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
RMRP	Cartilage-hair hypoplasia, Metaphyseal dysplasia without hypotrichosis, Anauxetic dysplasia	AR	87	123
RTEL1	Pulmonary fibrosis and/or bone marrow failure, Dyskeratosis congenita	AD/AR	58	51
SH2D1A	Lymphoproliferative syndrome	XL	21	129
SMARCAL1	Schimke immunoosseous dysplasia	AR	20	88
SP110	Hepatic venoocclusive disease with immunodeficiency	AR	8	8

SPINK5	Netherton syndrome	AR	29	85
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
STK4	T-cell immunodeficiency syndrome, recurrent infections, autoimmunity,	AR	3	7
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
TFRC	Immunodeficiency 46	AR	8	2
TNFRSF4	Immunodeficiency	AR	1	1
TYK2	Immunodeficiency	AR	9	9
UNC119	Immunodeficiency, Cone-rod dystrophy 2	AD	1	5
WAS	Neutropenia, severe congenital, Thrombocytopenia, Wiskott-Aldrich syndrome	XL	57	439
ZAP70	Selective T-cell defect	AR	15	29

*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
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	
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
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	
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	
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

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	
SH2D1A	ChrX:123499593	c.138-17_138-11delAGTTTAT	NM_002351.4	
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
TBX1	Chr22:19743578	c.-777C>T	NM_080647.1	
TBX1	Chr22:19743735	c.-620A>C	NM_080647.1	rs536892777
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: *CORO1A* (NM_007074:11), *IL12RB1* (NM_153701:10). 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 severe combined immunodeficiency panel covers classical genes associated with Wiskott-Aldrich syndrome, combined immunodeficiencies, Omenn syndrome, CD40 ligand deficiency, DOCK8 deficiency, complement receptor 3 deficiency, purine nucleoside phosphorylase PNP deficiency, STAT deficiencies and Job's 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	96.9% (7,563/7,806)	>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% (37/37)	

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 % (TP/(TP+FN)	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%)	92.3%(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 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 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 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 Severe Combined Immunodeficiency Panel

ICD-10	Disease
D82.0	Wiskott-Aldrich syndrome
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

- European Society for Immunodeficiencies
- GeneReviews - *WAS*-Related Disorders
- GeneReviews - Autosomal Dominant Hyper IgE Syndrome
- GeneReviews - Hyper IgM Syndrome
- GeneReviews - Job's Syndrome
- GeneReviews - Severe Combined Immune Deficiency
- GeneReviews - Wiskott-Aldrich Syndrome
- GeneReviews - X-Linked Hyper IgM Syndrome
- GeneReviews - X-Linked Severe Combined Immunodeficiency
- Immune Deficiency Foundation
- NORD - Hyper IgM Syndrome

- NORD - Job's Syndrome
- NORD - Severe Combined Immune Deficiency
- NORD - Wiskott-Aldrich Syndrome
- 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
- Wiskott-Aldrich Foundation