

Bardet-Biedl Syndrome Panel

Test code: KI0201

Is a 27 gene panel that includes assessment of non-coding variants.

Is ideal for patients with a clinical suspicion / diagnosis of Bardet-Biedl Syndrome or Alstrom Syndrome.

About Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is an important genetic cause of chronic kidney disease with end-stage renal disease (ESRD). It is a multi-system disorder consisting of obesity, retinal degeneration, cognitive impairment, genitourinary tract malformations and polydactyly. Polycystic kidneys are the most likely cause of premature death from the syndrome, followed by complications caused by obesity, including type II diabetes, hypertension and hypercholesterolaemia. Although BBS is considered to be a developmental disorder, the only clues in utero may be hexadactyly and hyperechoic kidneys. The diagnosis is often only established once the vision begins to degrade. The estimated prevalence of BBS is 1-9:1,000,000 and in Europe between 1:125,000 and 1:175,000. Genes associated with BBS code for proteins involved in the development and function of primary cilia and absence or dysfunction of BBS proteins results in ciliary anomalies. Recognition of the clinical picture is important as the diagnosis can be confirmed by molecular analysis, allowing appropriate genetic counseling for family members and possible prenatal diagnosis. Alström syndrome is an autosomal recessive disorder, which shares substantial overlap with Bardet-Biedl syndrome. It is characterised by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy, insulin resistance syndrome and developmental delay. Over 60% of individuals with Alström syndrome develop cardiac failure as a result of dilated cardiomyopathy at some stage of their lives. Males may have hypogonadotrophic hypogonadism. Renal disease may present as polyuria and polydipsia resulting from a urinary concentrating defect. ESRD can occur as early as the late teens. In contrast to BBS, Alström syndrome is characterised by relative preservation of cognitive function and the absence of polydactyly. Alström syndrome is caused by mutations in the gene *ALMS1*.

Availability

4 weeks

Gene Set Description

Genes in the Bardet-Biedl Syndrome Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ALMS1*	Alström syndrome	AR	197	302
ARL6	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	14	21
BBIP1#	Bardet-Biedl syndrome 18	AR	1	1
BBS1	Bardet-Biedl syndrome	AR	66	103
BBS10	Bardet-Biedl syndrome	AR	90	107
BBS12	Bardet-Biedl syndrome	AR	36	58
BBS2	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	58	91
BBS4	Bardet-Biedl syndrome	AR	25	53
BBS5	Bardet-Biedl syndrome	AR	18	31

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BBS7	Bardet-Biedl syndrome	AR	19	43
BBS9	Bardet-Biedl syndrome	AR	27	52
C8ORF37	Retinitis pigmentosa, Cone rod dystrophy, Bardet-Biedl syndrome 21	AR	8	17
CEP19	Morbid obesity and spermatogenic failure, Bardet-Biedl syndrome	AR	2	2
CEP290*	Bardet-Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Senior-Loken syndrome, Meckel syndrome	AR	130	289
CPE	Obesity, severe, and type II diabetes	AR		2
IFT172	Retinitis pigmentosa, Short -rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	22	25
IFT27	Bardet Biedl syndrome 19	AR	1	4
LZTFL1	Bardet-Biedl syndrome 17	AR	6	3
MKKS	Bardet-Biedl syndrome, McKusick-Kaufman syndrome	AR	21	59
MKS1	Bardet-Biedl syndrome, Meckel syndrome	AR	50	52
PNPLA6	Laurence-Moon syndrome, Boucher-Neuhauser syndrome, Spastic paraplegia 39	AR	26	58
SCAPER	Retinal dystrophy, Retinitis pigmentosa	AR	4	7
SDCCAG8	Bardet-Biedl syndrome, Senior-Loken syndrome	AR	14	18
TMEM67	Nephronophthisis, COACH syndrome, Joubert syndrome, Meckel syndrome	AR	87	170
TRIM32	Bardet-Biedl syndrome, Muscular dystrophy, limb-girdle	AR	13	16
TTC8	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	5	16
WDPCP	Meckel-Gruber syndrome, modifier, Bardet-Biedl syndrome, Congenital heart defects, hamartomas of tongue, and polysyndactyly	AR	6	8

*

Some, or all, of the gene is duplicated in the genome. [Read more.](#)

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The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#). Due to possible limitations these genes may not be available as single gene tests.

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database

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([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
BBS1	Chr11:66291105	c.951+58C>T	NM_024649.4	
BBS4	Chr15:73001820	c.77-216delA	NM_033028.4	rs113994189
BBS5	Chr2:170354110	c.619-27T>G	NM_152384.2	
CEP290	Chr12:88462434	c.6012-12T>A	NM_025114.3	rs752197734
CEP290	Chr12:88494960	c.2991+1655A>G	NM_025114.3	rs281865192
CEP290	Chr12:88508350	c.1910-11T>G	NM_025114.3	
CEP290	Chr12:88534822	c.103-18_103-13delGCTTTT	NM_025114.3	

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

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. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)

- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ± 20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test Performance

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

The performance metrics listed below are from an initial validation performed at our main laboratory in Finland. The performance metrics of our laboratory in Seattle, WA, are equivalent.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

	Sensitivity % (TP/(TP+FN))	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	99.2% (7,745/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA



Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Microdeletion/-duplication sdrs (large CNVs, n=37)		
Size range (0.1-47 Mb)	100% (25/25)	

The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics

Mean sequencing depth	143X
Nucleotides with >20x sequencing coverage (%)	99.86%

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	Specificity %
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%



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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 artificial mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

The target region for each gene includes coding exons and ± 20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding and regulatory variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the ‘Test limitations’ section above. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases including,



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but not limited, to [1000 Genomes Project](#), [gnomAD](#), [ClinVar](#) and [HGMD](#) into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as [SIFT](#), [PolyPhen](#), [MutationTaster](#) are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the crucial details of the analysis process.

Clinical Interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the [ACMG guideline 2015](#).

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

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, *in silico* predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references, abstracts and variant databases used to help ordering providers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. Our laboratory is therefore well-positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

CPT code(s) *

81404, 81406 x2, 81407, 81408, 81479

* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

ICD Codes

Refer to the most current version of ICD-10-CM manual for a complete list of ICD-10 codes.

Sample Requirements

- Blood (min. 1ml) in an EDTA tube
- Extracted DNA, min. 2 µg in TE buffer or equivalent
- Saliva (Please see [Sample Requirements](#) for accepted saliva kits)

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

We do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue. In addition, if the patient is affected with a hematological malignancy, DNA extracted from a non-hematological source (e.g. skin fibroblasts) is strongly recommended.

Please note that, in rare cases, mitochondrial genome (mtDNA) variants may not be detectable in blood or saliva in which case DNA extracted from post-mitotic tissue such as skeletal muscle may be a better option.

Read more about our sample requirements [here](#).

For Patients

Other

- [Alström Syndrome International](#)
- [American Academy of Ophthalmology, 2016: Recommendations of Clinical Assessment of Patients with Inherited Retinal Degeneration](#)
- [Bardet Biedl Syndrome Family Association](#)
- [GeneReviews - Bardet-Biedl Syndrome](#)
- [Genetic and Rare Diseases Information Center - BBS](#)
- [NORD - Bardet-Biedl Syndrome](#)