Blueprint Genetics

Abnormal Genitalia/ Disorders of Sex Development Panel

Test code: EN0201

Is a 73 gene panel that includes assessment of non-coding variants.

Is ideal for patients presenting with ambiguous genitalia, patients suspected to have a disorder of sexual development and patients suspected to have congenital adrenal hyperplasia (CAH).

About Abnormal Genitalia/ Disorders of Sex Development

Disorders of sex development (DSD) are a group of congenital conditions characterized by problems in the course of gender patterning, gonadal and sex development. It has been estimated that 1% – 2% of live births have some aspect of DSD. Approximately 5% of infants with DSD have ambiguous genitalia and indeterminate sex at birth. However, the vast majority of these patients do not require corrective surgery. Patients with 46,XY DSD have often impaired androgen synthesis or action and may have normal female external genitalia, while patients with 46,XX DSD conditions have often androgen excess. In 46,XX females, congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (21-OHD) is the most common cause of DSD. The estimated prevalence of CAH is 1:10,000 and 90%-95% of cases are due to mutations in *CYP21A2*. The severity of the condition often depends on the residual enzyme activity subdiving *CYP21A2* mutations in severe (classic phenotype, enzyme activity 0%-10%) and mild (non-classic, enzyme activity 20%-50%). Androgen insensitivity syndrome (AIS), caused by mutations in *AR*, is characterized by feminization of external genitalia and atypical sexual development in 46,XY individuals. The condition may be complete, partial or mild, depending on the level of androgen insensitivity. Mutations in the *AR* gene explain up to 95% of cases with complete androgen insensitivity, while the proportions are lower for the partial and mild subtypes. The combined prevalence of various AIS subtypes is estimated to be 5:100,000.

Availability

4 weeks

Gene Set Description

Genes in the Abnormal Genitalia/ Disorders of Sex Development Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
AMH	Persistent Mullerian duct syndrome	AR	5	56
AMHR2	Persistent Mullerian duct syndrome	AR	6	37
ANOS1*	Kallmann syndrome	XL/Digenic	36	186
AR	Androgen insensitivity, Hypospadias 1, X-linked	XL	147	612
ARX	Lissencephaly, Epileptic encephalopathy, Corpus callosum, agenesis of, with abnormal genitalia, Partington syndrome, Proud syndrome, Hydranencephaly with abnormal genitalia, Mental retardation	XL	66	93
ATRX	Carpenter-Waziri syndrome, Alpha-thalassemia/mental retardation syndrome, Holmes-Gang syndrome, Juberg-Marsidi syndrome, Smith-Fineman-Myers syndrome, Mental retardation-hypotonic facies syndrome	XL	65	165
BCOR	Microphthalmia, syndromic, Oculofaciocardiodental syndrome	XL	40	53
CDK9		AR		1

CDKN1C	Beckwith-Wiedemann syndrome, IMAGE syndrome	AD	35	81
CEP41	Joubert syndrome	AR/Digenic	7	11
CHD4	Sifrim-Hitz-Weiss syndrome	AD	14	21
CHD7	Isolated gonadotropin-releasing hormone deficiency, CHARGE syndrome	AD	276	860
CREBBP	Rubinstein-Taybi syndrome	AD	175	362
CYB5A	46, XY disorder of sex development, Methemoglobinemia, type IV	AR	3	5
CYP11A1	Adrenal insufficiency, congenital, with 46,XY sex reversal, partial or complete	AD/AR	14	28
CYP11B1*	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency, Glucocorticoid-remediable aldosteronism	AD/AR	55	147
CYP17A1	Adrenal hyperplasia, congenital, due to 17-alpha-hydroxylase deficiency	AR	35	126
CYP19A1	Aromatase deficiency, Aromatase excess syndrome	AR	17	52
CYP21A2*	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency, Hyperandrogenism, nonclassic , due to 21-hydroxylase deficiency	AR	48	296
DHCR7	Smith-Lemli-Opitz syndrome	AR	88	217
DHH	46,XY partial gonadal dysgenesis, with minifascicular neuropathy, 46,XY sex reversal 7	AD/AR	5	18
DYNC2H1	Short -rib thoracic dysplasia with or without polydactyly type 1, Short -rib thoracic dysplasia with or without polydactyly type 3, Asphyxiating thoracic dysplasia (ATD; Jeune), SRPS type 2 (Majewski)	AR/Digenic	148	205
ERCC3	Xeroderma pigmentosum, Trichothiodystrophy, photosensitive	AR	10	19
FEZF1	Hypogonadotropic hypogonadism 22 with or without anosmia, Kallmann syndrome	AR	2	3
FGF17	Hypogonadotropic hypogonadism 20, with or without anosmia	AD/Multigenic	2	5
FGF8	Hypogonadotropic hypogonadism	AD/Digenic	18	36
FGFR1	Pfeiffer syndrome, Trigonocephaly, Hypogonadotropic hypogonadism, Osteoglophonic Dwarfism - Craniostenosis, Hartsfield syndrome	AD/Digenic/Multigenic	72	257
FIG4	Amyotrophic lateral sclerosis, Polymicrogyria, bilateral occipital, Yunis-Varon syndrome, Charcot-Marie-Tooth disease	AD/AR	34	69
FRAS1	Fraser syndrome	AR	27	58
FSHB	Hypogonadotropic hypogonadism 24 without anosmia	AR	5	8
GATA4	Tetralogy of Fallot, Atrioventricular septal defect, Testicular anomalies with or without congenital heart disease, Ventricular septal defect, Atrial septal defect	AD	37	140

GNRH1	Hypogonadotropic hypogonadism 12 with or without anosmia	AR	1	10
GNRHR	Hypogonadotropic hypogonadism	AR	23	58
HS6ST1	Hypogonadotropic hypogonadism 15, with or without anosmia, Kallmann syndrome	AD		7
HSD17B3	Neurodevelopmental disorder with hypotonia, neonatal respiratory insufficiency, and thermodysregulation	AR	24	63
HSD3B2	3-beta-hydroxysteroid dehydrogenase, II deficiency	AR	11	63
IL17RD	Hypogonadotropic hypogonadism	AD/Digenic	6	10
IRF6	Orofacial cleft, Popliteal pterygium syndrome, van der Woude syndrome	AD	45	338
KISS1	Hypogonadotropic hypogonadism 13 with or without anosmia, Central precocious puberty	AR	1	10
KISS1R	Precocious puberty, central 1	AD/AR	7	36
LEP	Leptin deficiency	AR	5	20
LEPR	Leptin receptor deficiency	AR	4	30
LHB	Hypogonadotropic hypogonadism 23 with or without anosmia	AR	6	8
LHCGR	Precocious puberty, male, Leydig cell hypoplasia, Luteinizing hormone resistance, female	AR	34	76
MAMLD1	Hypospadias 2, X-linked	XL	5	20
MAP3K1	46,XY sex reversal 6	AD	9	27
MKRN3	Central precocious puberty	AD	6	32
MKS1	Bardet-Biedl syndrome, Meckel syndrome	AR	50	52
NR0B1	Adrenal hypoplasia, congenital, 46,XY sex reversal	XL	73	252
NR5A1	Adrenocortical insufficiency, Premature ovarian failure, 46,XY sex reversal	AD	28	183
NSMF	Hypogonadotropic hypogonadism 9 with or without anosmia	AD		8
POLR3B	Leukodystrophy, hypomyelinating	AR	19	58
POR	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency, Antley-Bixler syndrome	AR	14	70
PROK2	Hypogonadism, hypogonadotropic, Kallmann syndrome	AR	7	20
PROKR2	Hypogonadotropic hypogonadism	AR	9	54
PROP1	Pituitary hormone deficiency, combined	AR	33	37
RNF216*	Cerebellar ataxia and hypogonadotropic hypogonadism (Gordon Holmes syndrome)	AR	10	14

RSPO1	Palmoplantar hyperkeratosis with squamous cell carcinoma of skin and 46,XX sex reversal	AR	3	5
SAMD9	Mirage syndrome, Tumoral calcinosis, normophosphatemic	AD/AR	10	27
SGPL1	Nephrotic syndrome 14	AR	8	17
SOX10	Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease, Kallmann syndrome	AD	56	148
SOX2*	Microphthalmia, syndromic	AD	34	104
SOX9	Campomelic dysplasia, 46,XY sex reversal, Brachydactyly with anonychia (Cooks syndrome)	AD	47	144
SRD5A2	Steroid 5-alpha-reductase 2 deficiency	AR	45	119
SRY	46,XX disorder of sex development, 46,XY disorder of sex development	YL	29	109
STAR	Lipoid adrenal hyperplasia	AR	34	83
TAC3	Hypogonadotropic hypogonadism	AR	5	10
TACR3	Hypogonadotropic hypogonadism	AR	8	36
TOE1	Pontocerebellar hypoplasia type 7		11	12
TSPYL1	Sudden infant death with dysgenesis of the testes syndrome, 46, XY disorder of sex development	AR	1	8
WDR11	Hypogonadotropic hypogonadism, Kallmann syndrome	AD	3	17
WT1	Denys-Drash syndrome, Frasier syndrome, Wilms tumor, Nephrotic syndrome, type 4	AD	42	183
ZFPM2	46,XY sex reversal, Diaphragmatic hernia 3, Tetralogy of Fallot	AD/AR	9	50

*

Some, or all, of the gene is 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 (#). Due to possible limitations these genes may not be available as single gene tests.

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap

databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
AMH	Chr19:2249105		NM_000479.3	
AMHR2	Chr12:53819422	c.622-51C>T	NM_020547.2	
AMHR2	Chr12:53819426	c.622-47C>T	NM_020547.2	rs200782636
AR	ChrX:66764442	c.-547C>T	NM_000044.3	
AR	ChrX:66788676	c.1616+22072A>C	NM_000044.3	
AR	ChrX:66905841	c.1769-11T>A	NM_000044.3	
AR	ChrX:66942551	c.2450-118A>G	NM_000044.3	
AR	ChrX:66942627	c.2450-42G>A	NM_000044.3	
CDKN1C	Chr11:2905209	c.*5+20G>T	NM_000076.2	rs760540648
CHD7	Chr8:61734568	c.2836-15C>G	NM_017780.3	
CHD7	Chr8:61757794	c.5051-15T>A	NM_017780.3	
CHD7	Chr8:61763034	c.5405-18C>A	NM_017780.3	rs199981784
CHD7	Chr8:61763035	c.5405-17G>A	NM_017780.3	rs794727423
CHD7	Chr8:61763039	c.5405-13G>A	NM_017780.3	rs1131690787
CREBBP	Chr16:3788684	c.4281-11C>G	NM_004380.2	rs587783493
CYP11B1	Chr8:143958423	c.595+16G>T	NM_000497.3	
CYP21A2	Chr6:32006858	c.293-13C>G	NM_000500.7	rs6467
DYNC2H1	Chr11:103019205	c.2819-14A>G	NM_001080463.1	rs781091611
DYNC2H1	Chr11:103055609	c.6478-16G>A	NM_001080463.1	rs376892534
GATA4	Chr8:11561282	c.-989C>T	NM_002052.3	
GATA4	Chr8:11561369	c.-902G>T	NM_002052.3	
GATA4	Chr8:11561399		NM_002052.3	rs1195641788
GATA4	Chr8:11612500	c.910-55T>C	NM_002052.3	
GATA4	Chr8:11612745	c.997+103G>T	NM_002052.3	rs113049875
GATA4	Chr8:11614418	c.998-26G>A	NM_002052.3	
IRF6	Chr1:209975332	c.-19C>A	NM_006147.3	

IRF6	Chr1:209975361	c.-48A>T	NM_006147.3	
IRF6	Chr1:209979367	c.-151G>A	NM_006147.3	
IRF6	Chr1:209979435	c.-219C>T	NM_006147.3	
IRF6	Chr1:209989478	c.-10263dupT	NM_006147.3	
KISS1	Chr1:204165663	c.-198C>T	NM_002256.3	rs770004886
MKRN3	Chr15:23810776	c.-150_-147delTCAG	NM_005664.3	
MKRN3	Chr15:23810849	c.-81C>T	NM_005664.3	
POLR3B	Chr12:106804589	c.967-15A>G	NM_018082.5	
POLR3B	Chr12:106831447	c.1857-12A>G	NM_018082.5	rs528038639
POR	Chr7:75544501	c.-5+4A>G	NM_000941.2	
PROP1	Chr5:177420059	c.343-11C>G	NM_006261.4	
SOX10	Chr22:38379877	c.-84-2A>T	NM_006941.3	
SOX10	Chr22:38412215	c.-31954C>T	NM_006941.3	rs606231342
SOX10	Chr22:38412781	c.-32520C>G	NM_006941.3	rs533778281
SOX9	Chr17:70117348	c.-185G>A	NM_000346.3	
SRY	ChrY:2655719	c.-75G>A	NM_003140.2	
SRY	ChrY:2655774	c.-133_-131delAGG	NM_003140.2	
SRY	ChrY:2655774	c.-130G>C	NM_003140.2	
STAR	Chr8:38003676	c.466-11T>A	NM_000349.2	

Test Strength and Limitations

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

A significant proportion of pathogenic *CYP21A2* variants are secondary to gene conversions. We have been able to detect some gene conversions and some copy number variants in patients referred to clinical testing; however, we have not performed an analytic validation of these variant types and our detection capabilities are likely limited.
Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

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

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

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

Test Performance

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

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

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

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

Blueprint Genetics

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

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	99.2% (7,745/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
Size range (0.1-47 Mb)	100% (25/25)	
The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics		
Mean sequencing depth	143X	
Nucleotides with >20x sequencing coverage (%)	99.86%	

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	Specificity %
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%

Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	99,997%
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%

The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding and regulatory variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases including, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen,MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the crucial details of the analysis process.

Clinical Interpretation

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

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

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

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

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

Blueprint Genetics

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) *

81173, 81403, 81404 x4, 81405 x6, 81406 x4, 81407 x2, 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

- AIS - DSD Support Group
- AIS-DSD Support Group
- Accord Alliance
- Androgen Insensitivity SyndromeSupport Group
- Androgen Insensitivity Syndrome Support Group
- CAH support group
- CARES Foundation
- Congenital Adrenal Hyperplasia Education and Support Group
- Congenital Adrenal Hyperplasia education and support group
- GARD - Persistent Mullerian Duct Syndrome
- GeneReviews - 46,XY Disorder of Sex Development
- GeneReviews - Androgen Insensitivity Syndrome
- GeneReviews - Congenital Adrenal Hyperplasia
- Intersex Society of North America

- NORD - Androgen Insensitivity Syndrome
- NORD - Congenital Adrenal Hyperplasia
- NORD - Persistent Mullerian duct syndrome
- National Adrenal Diseases Foundation