# Donor 7256

# Genetic Testing Summary

Fairfax Cryobank recommends reviewing this genetic testing summary with your healthcare provider to determine suitability.

Last Updated: 12/10/24

Donor Reported Ancestry: German, Norwegian, Czech  Jewish Ancestry: No

| Genetic Test* | Result | Comments/Donor's Residual Risk** |
|---|---|---|
| Chromosome analysis (karyotype) | Normal male karyotype | No evidence of clinically significant chromosome abnormalities |
| Hemoglobin evaluation | Normal hemoglobin fractionation and MCV/MCH results | Reduced risk to be a carrier for sickle cell anemia, beta thalassemia, alpha thalassemia trait (aa/-- and a-/a-) and other hemoglobinopathies |
| Expanded Genetic Disease Carrier Screening Panel attached- 514 diseases by gene sequencing. | Carrier: CLN3-related conditions (CLN3)<br><br>Carrier: GBE1-related conditions (GBE1)<br><br>Carrier: Sepiapterin reductase deficiency (SPR)<br><br>Carrier: Congenital nephrotic syndrome type 2 (NPHS2) see page 7of the attached report.<br><br>Negative for other genes sequenced. | Partner testing is recommended before using this donor.<br><br>Residual risks for negative results can be seen here:<br><br>https://fairfaxcryobank.com/invitae-residual-risk-table |

*No single test can screen for all genetic disorders. A negative screening result significantly reduces, but cannot eliminate, the risk for these conditions in a pregnancy.

**Donor residual risk is the chance the donor is still a carrier after testing negative.

INVITAE

# INVITAE CARRIER SCREEN RESULTS

| | | | | | |
|---|---|---|---|---|---|
| **Patient name:** | Donor 7256 | **Sample type:** | Blood | **Report date:** | 27-DEC-2023 |
| **DOB:** | [redacted] | **Sample collection date:** | 19-DEC-2023 | **Invitae #:** | [redacted] |
| **Sex assigned at birth:** | Male | **Sample accession date:** | 20-DEC-2023 | **Clinical team:** | [redacted] |
| **Gender:** | Man | | | | |
| **Patient ID (MRN):** | [redacted] | | | | |

**Reason for testing**

Gamete donor

**Test performed**

Invitae Carrier Screen

## RESULT: POSITIVE

This carrier test evaluated 514 gene(s) for genetic changes (variants) that are associated with an increased risk of having a child with a genetic condition. Knowledge of carrier status for one of these conditions may provide information that can be used to assist with family planning and/or preparation. Carrier screening is not intended for diagnostic purposes. To identify a potential genetic basis for a condition in the individual being tested, diagnostic testing for the gene(s) of interest is recommended.

This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below. No other clinically significant changes were identified in the remaining genes evaluated with this test.

| RESULTS | GENE | VARIANT(S) | INHERITANCE | PARTNER TESTING RECOMMENDED |
|---|---|---|---|---|
| **Carrier:** CLN3-related conditions | CLN3 | Deletion (Exons 8-9) | Autosomal recessive | Yes |
| **Carrier:** GBE1-related conditions | GBE1 | c.691+2T>C (Splice donor) | Autosomal recessive | Yes |
| **Carrier:** Sepiapterin reductase deficiency | SPR | c.751A>T (p.Lys251*) | Autosomal recessive | Yes |

## Next steps

- See the table above for recommendations regarding testing of this individual's reproductive partner.
- Even for genes that have a negative test result, there is always a small risk that an individual could still be a carrier. This is called “residual risk.” See the Carrier detection rates and residual risks document.
- Discussion with a physician and/or genetic counselor is recommended to further review the implications of this test result and to understand these results in the context of any family history of a genetic condition.
- All patients, regardless of result, may wish to consider additional screening for hemoglobinopathies by complete blood count (CBC) and hemoglobin electrophoresis, if this has not already been completed.
- Individuals can register their tests at **https://www.invitae.com/patients/** to access online results, educational resources, and next steps.

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# Clinical summary

## RESULT: CARRIER

### CLN3-related conditions

A single Pathogenic variant, Deletion (Exons 8-9), was identified in CLN3.

**What are CLN3-related conditions?**

CLN3-related conditions include ceroid lipofuscinosis, neuronal type 3 (CLN3) and nonsyndromic retinitis pigmentosa (RP). Neuronal ceroid lipofuscinosis (NCL) is a group of related conditions resulting from dysfunction of lysosomes, which are structures in the cell that break down and recycle other molecules. NCLs primarily affect the brain. RP is a group of conditions that causes vision impairment. RP can be caused by changes in many different genes.

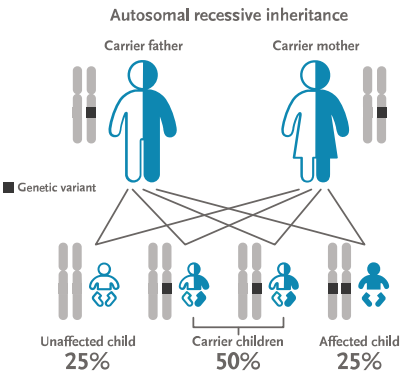
CLN3 is a neurodegenerative condition resulting from storage material damaging brain cells (cerebral and cerebellar atrophy). Classic juvenile CLN3 typically presents between the ages of four and ten with rapidly progressive vision loss. As the condition progresses, affected individuals experience seizures, loss of motor skills which causes problems with balance and coordination (ataxia), and loss of cognitive abilities. Psychiatric and behavioral changes have also been reported. Life span is reduced, with most individuals living into the second or third decade. Cases of affected individuals with slower disease progression and of disease onset in infancy have also been reported.

RP is characterized by progressive degeneration of the light-sensitive tissue that lines the back of the eye (retina). The first symptom is often difficulty seeing in low light settings (night blindness), which usually occurs during childhood or adolescence. Vision loss continues over years or decades and typically progresses to a loss of side (peripheral) vision, causing tunnel vision. Ultimately, central vision loss occurs. Many individuals with RP are legally blind by adulthood, though the severity of symptoms and age of onset varies by individual. Intelligence and life expectancy are not typically affected.

Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

## Next steps

Carrier testing for the reproductive partner is recommended.




**If your partner tests positive:**

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the CLN3 gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

**If your partner tests negative:**

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for CLN3-related conditions. These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| CLN3-related conditions (AR)<br>NM_001042432.1 | CLN3 | Pan-ethnic | 1 in 230 | 1 in 22900 |

## RESULT: CARRIER

# GBE1-related conditions

A single Pathogenic variant, c.691+2T>C (Splice donor), was identified in GBE1.

### What are GBE1-related conditions?

GBE1-related conditions include glycogen storage disease type IV (GSD IV) and adult polyglucosan body disease (APBD). GSD is a group of conditions in which individuals have difficulty breaking down a complex sugar called glycogen. A buildup of glycogen impairs the function of certain organs and tissues. APBD is a condition that affects the nervous system.

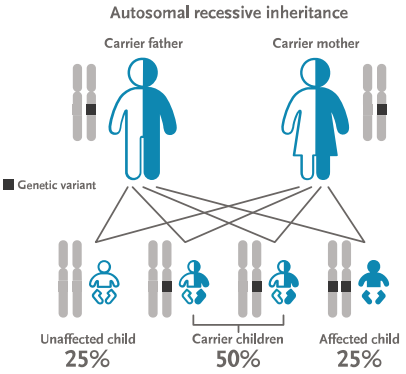
GSD IV may the affect the liver, heart, muscles, and other parts of the body. There is broad variability of symptoms and severity, even between family members with the same genetic change. The most common form of GSD IV is the classic (progressive) hepatic type. Symptoms typically present during the first few months of life and include poor growth (failure to thrive) and enlarged liver (hepatomegaly). Children often also have a weakened heart muscle (cardiomyopathy), low muscle tone (hypotonia), liver damage (cirrhosis) due to the formation of scar tissue in the liver, and additional liver and other findings. Many affected children die before the age of 5 years from liver failure. The non-progressive hepatic type is similar to the classic (progressive) type; however, the liver disease is less severe and cirrhosis usually does not develop. Other symptoms include hypotonia and muscle weakness (myopathy). Most affected individuals survive into adulthood; life span depends on the severity of symptoms. The neuromuscular forms of GSD IV may have symptoms that are noticeable before or at birth, or not until later in childhood. Symptoms of the earliest onset forms may include excess amniotic fluid (polyhydramnios), excess fluid accumulation in the body (fetal hydrops), lack of movement (fetal akinesia) that leads to joint deformities that restrict movement of the hands and feet (arthrogryposis), severe hypotonia, muscle wasting (amyotrophy), and enlarged and weakened heart muscle (dilated cardiomyopathy). Infants with the earliest onset forms typically die during the newborn period or first few months of life from heart or breathing problems. Symptoms of the childhood onset form typically include myopathy and dilated cardiomyopathy. While some affected individuals have only mild, progressive myopathy, others may die in early adulthood from severe cardiomyopathy.

Symptoms of APBD typically present between the ages of 40 and 60 and include bladder control problems, reduced sensation in the legs due to nerve damage (peripheral neuropathy), and abnormal muscle tensing (spasticity) and weakness that cause difficulty walking. Most affected individuals eventually develop damage to the autonomic nervous system, which controls involuntary body processes, leading to loss of bladder and bowel control and control over limb function, as well as problems with heart and breathing rates, blood pressure, and temperature regulation. Some may also experience cognitive difficulty. Life span may be shortened.

Individuals with GSD IV who have severe liver or heart disease may require organ transplantation. Some individuals with APBD eventually require walking aids or wheelchair assistance. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

## Next steps

Carrier testing for the reproductive partner is recommended.




### If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the GBE1 gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

### If your partner tests negative:

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for GBE1-related conditions. These values are provided only as a guide, are based on the detection rate for the

condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| GBE1-related conditions (AR)<br>NM_000158.3 | GBE1 | Pan-ethnic | 1 in 387 | 1 in 38600 |

## RESULT: CARRIER

# Sepiapterin reductase deficiency

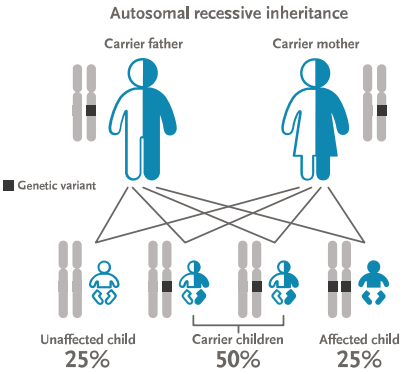
A single Pathogenic variant, c.751A>T (p.Lys251*), was identified in SPR.

### What is sepiapterin reductase deficiency ?

Sepiapterin reductase (SPR) deficiency is a condition that primarily impacts the nervous system. SPR deficiency is caused by a shortage of tetrahydrobiopterin (BH4). There are multiple forms of BH4 deficiency, which are caused by changes in several different genes. Shortage of BH4 leads to reduced levels of certain chemicals in the brain that pass signals between nerve cells (neurotransmitters) including serotonin and dopamine. Unlike other forms of BH4 deficiency, SPR deficiency is not associated with increased levels of the amino acid phenylalanine in the body. Symptoms of SPR deficiency are highly variable but typically begin early in life. Affected individuals develop a movement disorder caused by abnormal muscle tensing (dystonia), which is responsive to dopamine, described as dopa-responsive dystonia. This is characterized by abnormal, often repetitive patterned or twisting movements and/or postures. Other symptoms of SPR deficiency include low muscle tone, particularly affecting the torso (axial hypotonia), motor and language delays, episodic and involuntary upward rotation of the eyes (oculogyric crises), and generalized weakness. Some affected individuals may have Parkinsonian tremors, increased muscle tone in the limbs (hypertonia), increased reflexes (hyperreflexia), intellectual disability, psychiatric and/or behavioral issues, and/or problems with the autonomic nervous system, which controls involuntary body processes such as the regulation of breathing rate and body temperature (autonomic dysfunction). Affected individuals seem to have a daily pattern of symptoms (diurnal fluctuations) and increased sleep may help improve symptoms. Prognosis is dependent upon the severity of symptoms. Follow-up depends on each affected individual's specific situation, and discussion with a healthcare provider should be considered.

## Next steps

Carrier testing for the reproductive partner is recommended.




### If your partner tests positive:

In autosomal recessive inheritance, an individual must have disease-causing genetic changes in each copy of the SPR gene to be affected. Carriers, who have a disease-causing genetic change in only one copy of the gene, typically do not have symptoms. When both reproductive partners are carriers of an autosomal recessive condition, there is a 25% chance for each child to have the condition.

### If your partner tests negative:

A negative carrier test result reduces, but does not eliminate, the chance that a person may be a carrier. The risk that a person could still be a carrier, even after a negative test result, is called a residual risk. See the table below for your partner's hypothetical residual risk after testing negative for sepiapterin reductase deficiency . These values are provided only as a guide, are based on the detection rate for the condition as tested at Invitae, and assume a negative family history, the absence of symptoms, and vary based on the ethnic background of an individual. For genes associated with both dominant and recessive inheritance, the numbers provided apply to the recessive condition(s) associated with the gene.

| DISORDER (INHERITANCE) | GENE | ETHNICITY | CARRIER FREQUENCY BEFORE SCREENING | CARRIER RESIDUAL RISK AFTER NEGATIVE RESULT |
|---|---|---|---|---|
| Sepiapterin reductase deficiency (AR) NM_003124.4 | SPR | Pan-ethnic | ≤1 in 500 | Reduced |

## Results to note

### ABCA4

- c.5603A>T (p.Asn1868Ile) was identified in the ABCA4 gene.
- This benign variant is not known to cause disease and does not impact this individual's risk to be a carrier for ABCA4-related conditions. Carrier testing for the reproductive partner is not indicated based on this result. See Variant details for more information.

### NPHS2

- c.686G>A (p.Arg229Gln) , was identified in NPHS2. This variant may be pathogenic when in combination with certain NPHS2 variants, and therefore its clinical significance is currently uncertain.

- Please note that the c.686G>A (p.Arg229Gln) variant may be pathogenic when on the opposite chromosome (in trans) from certain other NPHS2 variants. The c.686G>A (p.Arg229Gln) variant is unlikely to be associated with nephrotic syndrome when homozygous (two copies).

  If identified, pathogenic NPHS2 variant(s) would be included in the Clinical summary section. Additionally, when the combination of a pathogenic NPHS2 variant and c.686G>A (p.Arg229Gln) has been reported to be clinically significant, this would be described in the Variant details for the pathogenic variant.

  Congenital nephrotic syndrome type 2 (NPHS2), also called steroid-resistant nephrotic syndrome, is a condition in which the kidneys are unable to properly filter waste products from the blood and remove them in the urine. The combination of c.686G>A (p.Arg229Gln) and certain other NPHS2 variants is associated with a form of the condition which has later onset and slower disease progression.

  Carrier testing for the reproductive partner may be considered, since c.686G>A (p.Arg229Gln) may be pathogenic when on the opposite chromosome from certain other NPHS2 variants.

### SMN1

- Negative result. SMN1: 2 copies; c.*3+80T>G not detected.

### Pseudodeficiency allele(s)

- Benign changes, c.742G>A (p.Asp248Asn), c.550C>T (p.Arg184Cys) and c.1685T>C (p.Ile562Thr), known to be pseudodeficiency alleles, identified in the GALC gene. Pseudodeficiency alleles are not known to be associated with disease, including Krabbe disease.
- The presence of a pseudodeficiency allele does not impact this individual's risk to be a carrier. Individuals with pseudodeficiency alleles may exhibit false positive results on related biochemical tests, including newborn screening. However, pseudodeficiency alleles are not known to cause disease, even when there are two copies of the variant (homozygous) or when in combination with another disease-causing variant (compound heterozygous). Carrier testing for the reproductive partner is not indicated based on this result.

## Variant details

ABCA4, Exon 40, c.5603A>T (p.Asn1868Ile), heterozygous, Benign (reportable variant)

- This sequence change replaces asparagine, which is neutral and polar, with isoleucine, which is neutral and non-polar, at codon 1868 of the ABCA4 protein (p.Asn1868Ile).
- This variant is present in population databases (rs1801466, gnomAD 7%), including several hundred presumably unaffected homozygous individuals.

- This missense change has been observed in individual(s) with late onset Stargardt disease with foveal sparing. However, the vast majority (estimated 95%) of homozygous and compound heterozygous individuals remain unaffected with penetrance ranging from 0.24% to 9.54% across published studies. This variant may modify disease severity and/or age of onset when it is present in combination with additional known pathogenic variants (e.g., when this variant is on the same chromosome as one or more deleterious variants, such as c.2588G>C, c.5461-10T>C, c.4496G>A, and/or c.2564G>A, and also on the opposite chromosome with a pathogenic variant). In other cases, disease progression is not impacted when this variant is one component of other complex alleles, such as with c.769-784C>T (PMID: 11328725, 28446513, 29971439, 30204727, 30480704, 30670881, 31614660, 31618761, 31884623, 32037395, 32307445, 32815999, 34440414, 34874912).
- ClinVar contains an entry for this variant (Variation ID: 99390).
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invitae indicates that this missense variant is expected to disrupt ABCA4 protein function with a positive predictive value of 95%.
- Experimental studies are conflicting or provide insufficient evidence to determine the effect of this variant on ABCA4 function (PMID: 11017087, 32845050, 33375396).
- For these reasons, this variant has been classified as a Benign reportable variant.

### CLN3, Deletion (Exons 8-9), heterozygous, PATHOGENIC

- This variant is a gross deletion of the genomic region encompassing exon(s) 8-9 of the CLN3 gene. This deletion is out-of-frame, and is expected to create a premature termination codon and result in an absent or disrupted protein product. Loss-of-function variants in CLN3 are known to be pathogenic (PMID: 9311735, 28542676).
- A similar copy number variant has been observed in individuals with juvenile neuronal ceroid lipofuscinosis, also known as Batten disease, and accounts for between 81-85% of all disease-causing alleles. (PMID: 7553855, 20187884, 21228398, 21990111, 23374165).
- This variant is also known as deletion of exons 7-8.
- Algorithms developed to predict the effect of variants on protein structure and function are not available or were not evaluated for this variant.
- Experimental studies have shown that a similar copy number variant affects CLN3 function (PMID: 10332042, 17947292, 19132115).
- For these reasons, this variant has been classified as Pathogenic.

### GBE1, Intron 5, c.691+2T>C (Splice donor), heterozygous, PATHOGENIC

- This sequence change affects a donor splice site in intron 5 of the GBE1 gene. It is expected to disrupt RNA splicing. Variants that disrupt the donor or acceptor splice site typically lead to a loss of protein function (PMID: 16199547), and loss-of-function variants in GBE1 are known to be pathogenic (PMID: 15452297, 20058079).
- This variant is present in population databases (rs192044702, gnomAD 0.1%), and has an allele count higher than expected for a pathogenic variant.
- Disruption of this splice site has been observed in individual(s) with glycogen storage disease type IV (PMID: 19813197, 23218673, 26166723, 30569318). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant. It has also been observed to segregate with disease in related individuals.
- ClinVar contains an entry for this variant (Variation ID: 208584).
- Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- For these reasons, this variant has been classified as Pathogenic.

### SPR, Exon 3, c.751A>T (p.Lys251*), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Lys251*) in the SPR gene. While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 11 amino acid(s) of the SPR protein.
- This variant is present in population databases (rs121917747, gnomAD 0.01%).
- This premature translational stop signal has been observed in individual(s) with SPR-related conditions (PMID: 16917893, 18502672, 21431957, 21677200, 24212389, 25763508, 29116116). In at least one individual the data is consistent with being in trans (on the opposite chromosome) from a pathogenic variant.
- ClinVar contains an entry for this variant (Variation ID: 12944).
- For these reasons, this variant has been classified as Pathogenic.

## Residual risk

No carrier test can detect 100% of carriers. There still remains a small risk of being a carrier after a negative test (residual risk). Residual risk values assume a negative family history and are inferred from published carrier frequencies and estimated detection rates based on testing technologies used at Invitae. You can view Invitae's complete Carrier detection rates and residual risks document (containing all carrier genes) online at https://www.invitae.com/carrier-residual-risks/. Additionally, the order-specific information for this report is available to download in the portal (under this order's documents) or can be requested by contacting Invitae Client Services. The complete Carrier detection rates and residual risks document will not be applicable for any genes with specimen-specific limitations in sequencing and/or deletion/duplication coverage. Please see the final bullet point in the Limitations section of this report to view if this specimen had any gene-specific coverage gaps.

## Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details. Results are negative, unless otherwise indicated in the report.

| GENE | TRANSCRIPT |
|---|---|
| AAAS | NM_015665.5 |
| ABCA12 | NM_173076.2 |
| ABCA3 | NM_001089.2 |
| ABCA4 | NM_000350.2 |
| ABCB11 | NM_003742.2 |
| ABCB4 | NM_000443.3 |
| ABCC2* | NM_000392.4 |
| ABCC8 | NM_000352.4 |
| ACAD9 | NM_014049.4 |
| ACADM | NM_000016.5 |
| ACADVL | NM_000018.3 |
| ACAT1 | NM_000019.3 |
| ACOX1 | NM_004035.6 |
| ACSF3 | NM_174917.4 |
| ADA | NM_000022.2 |
| ADAMTS2 | NM_014244.4 |
| ADAMTSL4 | NM_019032.5 |
| ADGRG1 | NM_005682.6 |
| ADGRV1 | NM_032119.3 |
| AGA | NM_000027.3 |
| AGL | NM_000642.2 |
| AGPS | NM_003659.3 |
| AGXT | NM_000030.2 |
| AHI1 | NM_017651.4 |
| AIPL1* | NM_014336.4 |
| AIRE | NM_000383.3 |
| ALDH3A2 | NM_000382.2 |
| ALDH7A1 | NM_001182.4 |
| ALDOB | NM_000035.3 |
| ALG1 | NM_019109.4 |
| ALG6 | NM_013339.3 |
| ALMS1 | NM_015120.4 |
| ALPL | NM_000478.5 |
| AMN* | NM_030943.3 |
| AMT | NM_000481.3 |
| ANO10* | NM_018075.3 |
| AP1S1 | NM_001283.3 |
| AQP2 | NM_000486.5 |
| ARG1 | NM_000045.3 |
| ARL6 | NM_177976.2 |
| ARSA | NM_000487.5 |
| ARSB | NM_000046.3 |
| ASL | NM_000048.3 |
| ASNS | NM_133436.3 |
| ASPA | NM_000049.2 |
| ASS1 | NM_000050.4 |
| ATM* | NM_000051.3 |
| ATP6V1B1 | NM_001692.3 |
| ATP7B | NM_000053.3 |
| ATP8B1* | NM_005603.4 |
| BBS1 | NM_024649.4 |
| BBS10 | NM_024685.3 |
| BBS12 | NM_152618.2 |
| BBS2 | NM_031885.3 |
| BBS4 | NM_033028.4 |
| BBS5 | NM_152384.2 |
| BBS7 | NM_176824.2 |
| BBS9* | NM_198428.2 |
| BCKDHA | NM_000709.3 |
| BCKDHB | NM_183050.2 |
| BCS1L | NM_004328.4 |
| BLM | NM_000057.3 |
| BLOC1S3 | NM_212550.4 |
| BLOC1S6 | NM_012388.3 |
| BMP1 | NM_006129.4;NM_001199.3 |
| BRIP1 | NM_032043.2 |
| BSND | NM_057176.2 |
| BTD | NM_000060.3 |
| CAD | NM_004341.4 |
| CANT1 | NM_138793.3 |
| CAPN3 | NM_000070.2 |
| CASQ2 | NM_001232.3 |
| CBS | NM_000071.2 |
| CC2D1A | NM_017721.5 |
| CC2D2A | NM_001080522.2 |
| CCDC103 | NM_213607.2 |
| CCDC39 | NM_181426.1 |
| CCDC88C | NM_001080414.3 |
| CD3D | NM_000732.4 |
| CD3E | NM_000733.3 |
| CD40 | NM_001250.5 |
| CD59 | NM_203330.2 |
| CDH23 | NM_022124.5 |
| CEP152 | NM_014985.3 |
| CEP290 | NM_025114.3 |
| CERKL | NM_001030311.2 |
| CFTR* | NM_000492.3 |
| CHAT | NM_020549.4 |
| CHRNE | NM_000080.3 |
| CHRNG | NM_005199.4 |
| CIITA | NM_000246.3 |
| CLCN1 | NM_000083.2 |
| CLN3 | NM_001042432.1 |
| CLN5 | NM_006493.2 |
| CLN6 | NM_017882.2 |
| CLN8 | NM_018941.3 |
| CLRN1 | NM_174878.2 |
| CNGB3 | NM_019098.4 |
| COL11A2* | NM_080680.2 |
| COL17A1 | NM_000494.3 |
| COL27A1 | NM_032888.3 |
| COL4A3 | NM_000091.4 |
| COL4A4 | NM_000092.4 |
| COL7A1 | NM_000094.3 |
| COX15 | NM_004376.6 |
| CPS1 | NM_001875.4 |
| CPT1A | NM_001876.3 |
| CPT2 | NM_000098.2 |

| GENE | TRANSCRIPT |
|---|---|
| CRB1 | NM_201253.2 |
| CRTAP | NM_006371.4 |
| CTNS | NM_004937.2 |
| CTSA | NM_000308.3 |
| CTSC | NM_001814.5 |
| CTSD | NM_001909.4 |
| CTSK | NM_000396.3 |
| CYBA | NM_000101.3 |
| CYP11A1 | NM_000781.2 |
| CYP11B1 | NM_000497.3 |
| CYP11B2 | NM_000498.3 |
| CYP17A1 | NM_000102.3 |
| CYP19A1 | NM_031226.2 |
| CYP1B1 | NM_000104.3 |
| CYP21A2* | NM_000500.7 |
| CYP27A1 | NM_000784.3 |
| CYP27B1 | NM_000785.3 |
| CYP7B1 | NM_004820.3 |
| DBT | NM_001918.3 |
| DCAF17 | NM_025000.3 |
| DCLRE1C | NM_001033855.2 |
| DDX11* | NM_030653.3 |
| DFNB59 | NM_001042702.3 |
| DGAT1 | NM_012079.5 |
| DGUOK | NM_080916.2 |
| DHCR7 | NM_001360.2 |
| DHDDS | NM_024887.3 |
| DLD | NM_000108.4 |
| DLL3 | NM_016941.3 |
| DNAH11 | NM_001277115.1 |
| DNAH5 | NM_001369.2 |
| DNAI1 | NM_012144.3 |
| DNAI2 | NM_023036.4 |
| DNMT3B | NM_006892.3 |
| DOK7 | NM_173660.4 |
| DUOX2* | NM_014080.4 |
| DYNC2H1 | NM_001080463.1 |
| DYSF | NM_003494.3 |
| EIF2AK3 | NM_004836.6 |

| GENE | TRANSCRIPT |
|---|---|
| EIF2B1 | NM_001414.3 |
| EIF2B2 | NM_014239.3 |
| EIF2B3 | NM_020365.4 |
| EIF2B4 | NM_015636.3 |
| EIF2B5 | NM_003907.2 |
| ELP1 | NM_003640.3 |
| EPG5 | NM_020964.2 |
| ERCC2 | NM_000400.3 |
| ERCC6 | NM_000124.3 |
| ERCC8 | NM_000082.3 |
| ESCO2 | NM_001017420.2 |
| ETFA | NM_000126.3 |
| ETFB | NM_001985.2 |
| ETFDH | NM_004453.3 |
| ETHE1 | NM_014297.3 |
| EVC | NM_153717.2 |
| EVC2 | NM_147127.4 |
| EXOSC3 | NM_016042.3 |
| EYS* | NM_001142800.1 |
| FAH* | NM_000137.2 |
| FAM161A | NM_001201543.1 |
| FANCA | NM_000135.2 |
| FANCC | NM_000136.2 |
| FANCD2* | NM_033084.3 |
| FANCE | NM_021922.2 |
| FANCG | NM_004629.1 |
| FANCI | NM_001113378.1 |
| FANCL* | NM_018062.3 |
| FBP1 | NM_000507.3 |
| FBXO7 | NM_012179.3 |
| FH* | NM_000143.3 |
| FKBP10 | NM_021939.3 |
| FKRP | NM_024301.4 |
| FKTN | NM_001079802.1 |
| FMO3 | NM_006894.6 |
| FOXN1 | NM_003593.2 |
| FOXRED1 | NM_017547.3 |
| FRAS1 | NM_025074.6 |
| FREM2 | NM_207361.5 |

| GENE | TRANSCRIPT |
|---|---|
| FUCA1 | NM_000147.4 |
| G6PC | NM_000151.3 |
| G6PC3 | NM_138387.3 |
| GAA | NM_000152.3 |
| GALC* | NM_000153.3 |
| GALE* | NM_000403.3 |
| GALK1 | NM_000154.1 |
| GALNS | NM_000512.4 |
| GALNT3 | NM_004482.3 |
| GALT | NM_000155.3 |
| GAMT | NM_000156.5 |
| GATM | NM_001482.2 |
| GBA* | NM_001005741.2 |
| GBE1 | NM_000158.3 |
| GCDH | NM_000159.3 |
| GCH1 | NM_000161.2 |
| GDF5 | NM_000557.4 |
| GFM1 | NM_024996.5 |
| GHR* | NM_000163.4 |
| GJB2 | NM_004004.5 |
| GLB1 | NM_000404.2 |
| GLDC | NM_000170.2 |
| GLE1 | NM_001003722.1 |
| GNE* | NM_001128227.2 |
| GNPAT | NM_014236.3 |
| GNPTAB | NM_024312.4 |
| GNPTG | NM_032520.4 |
| GNS | NM_002076.3 |
| GORAB | NM_152281.2 |
| GRHPR | NM_012203.1 |
| GRIP1 | NM_021150.3 |
| GSS | NM_000178.2 |
| GUCY2D | NM_000180.3 |
| GUSB | NM_000181.3 |
| HADH | NM_005327.4 |
| HADHA | NM_000182.4 |
| HADHB | NM_000183.2 |
| HAMP | NM_021175.2 |
| HAX1 | NM_006118.3 |

| GENE | TRANSCRIPT |
|---|---|
| HBA1* | NM_000558.4 |
| HBA2* | NM_000517.4 |
| HBB | NM_000518.4 |
| HEXA | NM_000520.4 |
| HEXB | NM_000521.3 |
| HGSNAT | NM_152419.2 |
| HJV | NM_213653.3 |
| HLCS | NM_000411.6 |
| HMGCL | NM_000191.2 |
| HMOX1 | NM_002133.2 |
| HOGA1 | NM_138413.3 |
| HPD | NM_002150.2 |
| HPS1 | NM_000195.4 |
| HPS3 | NM_032383.4 |
| HPS4 | NM_022081.5 |
| HPS5 | NM_181507.1 |
| HPS6 | NM_024747.5 |
| HSD17B3 | NM_000197.1 |
| HSD17B4 | NM_000414.3 |
| HSD3B2 | NM_000198.3 |
| HYAL1 | NM_153281.1 |
| HYLS1 | NM_145014.2 |
| IDUA | NM_000203.4 |
| IGHMBP2 | NM_002180.2 |
| IKBKB | NM_001556.2 |
| IL7R | NM_002185.3 |
| INVS | NM_014425.3 |
| ITGA6 | NM_000210.3 |
| ITGB3 | NM_000212.2 |
| ITGB4 | NM_001005731.2 |
| IVD | NM_002225.3 |
| JAK3 | NM_000215.3 |
| KCNJ1 | NM_000220.4 |
| KCNJ11 | NM_000525.3 |
| LAMA2 | NM_000426.3 |
| LAMA3 | NM_000227.4 |
| LAMB3 | NM_000228.2 |
| LAMC2 | NM_005562.2 |
| LARGE1 | NM_004737.4 |

| GENE | TRANSCRIPT |
|---|---|
| LCA5 | NM_181714.3 |
| LDLR | NM_000527.4 |
| LDLRAP1 | NM_015627.2 |
| LHX3 | NM_014564.4 |
| LIFR* | NM_002310.5 |
| LIG4 | NM_002312.3 |
| LIPA | NM_000235.3 |
| LMBRD1 | NM_018368.3 |
| LOXHD1 | NM_144612.6 |
| LPL | NM_000237.2 |
| LRAT | NM_004744.4 |
| LRP2 | NM_004525.2 |
| LRPPRC | NM_133259.3 |
| LYST | NM_000081.3 |
| MAK | NM_001242957.2 |
| MAN2B1 | NM_000528.3 |
| MANBA | NM_005908.3 |
| MCEE | NM_032601.3 |
| MCOLN1 | NM_020533.2 |
| MCPH1 | NM_024596.4 |
| MECR | NM_016011.3 |
| MED17 | NM_004268.4 |
| MESP2 | NM_001039958.1 |
| MFSD8 | NM_152778.2 |
| MKKS | NM_018848.3 |
| MKS1 | NM_017777.3 |
| MLC1* | NM_015166.3 |
| MLYCD | NM_012213.2 |
| MMAA | NM_172250.2 |
| MMAB | NM_052845.3 |
| MMACHC | NM_015506.2 |
| MMADHC | NM_015702.2 |
| MOCS1 | NM_001358530.2 |
| MOCS2A | NM_176806.3 |
| MOCS2B | NM_004531.4 |
| MPI | NM_002435.2 |
| MPL | NM_005373.2 |
| MPV17 | NM_002437.4 |
| MRE11 | NM_005591.3 |

| GENE | TRANSCRIPT |
|---|---|
| MTHFR* | NM_005957.4 |
| MTR | NM_000254.2 |
| MTRR | NM_002454.2 |
| MTTP | NM_000253.3 |
| MUSK | NM_005592.3 |
| MUT | NM_000255.3 |
| MVK | NM_000431.3 |
| MYO15A | NM_016239.3 |
| MYO7A | NM_000260.3 |
| NAGA | NM_000262.2 |
| NAGLU | NM_000263.3 |
| NAGS | NM_153006.2 |
| NBN | NM_002485.4 |
| NCF2 | NM_000433.3 |
| NDRG1 | NM_006096.3 |
| NDUFAF2 | NM_174889.4 |
| NDUFAF5 | NM_024120.4 |
| NDUFS4 | NM_002495.3 |
| NDUFS6 | NM_004553.4 |
| NDUFS7 | NM_024407.4 |
| NDUFV1 | NM_007103.3 |
| NEB* | NM_001271208.1 |
| NEU1 | NM_000434.3 |
| NGLY1 | NM_018297.3 |
| NPC1 | NM_000271.4 |
| NPC2 | NM_006432.3 |
| NPHP1 | NM_000272.3 |
| NPHS1 | NM_004646.3 |
| NPHS2 | NM_014625.3 |
| NR2E3 | NM_014249.3 |
| NSMCE3 | NM_138704.3 |
| NTRK1 | NM_001012331.1 |
| OAT* | NM_000274.3 |
| OCA2 | NM_000275.2 |
| OPA3 | NM_025136.3 |
| OSTM1 | NM_014028.3 |
| OTOA* | NM_144672.3 |
| OTOF | NM_194248.2;NM_194323.2 |
| P3H1 | NM_022356.3 |

| GENE | TRANSCRIPT |
|---|---|
| PAH | NM_000277.1 |
| PANK2 | NM_153638.2 |
| PC | NM_000920.3 |
| PCBD1 | NM_000281.3 |
| PCCA | NM_000282.3 |
| PCCB | NM_000532.4 |
| PCDH15 | NM_033056.3 |
| PCNT | NM_006031.5 |
| PDHB | NM_000925.3 |
| PEPD | NM_000285.3 |
| PET100 | NM_001171155.1 |
| PEX1* | NM_000466.2 |
| PEX10 | NM_153818.1 |
| PEX12 | NM_000286.2 |
| PEX13 | NM_002618.3 |
| PEX16 | NM_004813.2 |
| PEX2 | NM_000318.2 |
| PEX26 | NM_017929.5 |
| PEX5 | NM_001131025.1 |
| PEX6 | NM_000287.3 |
| PEX7 | NM_000288.3 |
| PFKM | NM_000289.5 |
| PGM3 | NM_001199917.1 |
| PHGDH | NM_006623.3 |
| PHKB | NM_000293.2;NM_001031835.2 |
| PHKG2 | NM_000294.2 |
| PHYH | NM_006214.3 |
| PIGN | NM_176787.4 |
| PKHD1* | NM_138694.3 |
| PLA2G6 | NM_003560.2 |
| PLEKHG5 | NM_020631.4 |
| PLOD1 | NM_000302.3 |
| PMM2 | NM_000303.2 |
| PNPO | NM_018129.3 |
| POLG | NM_002693.2 |
| POLH | NM_006502.2 |
| POMGNT1 | NM_017739.3 |
| POMT1 | NM_007171.3 |
| POMT2 | NM_013382.5 |

| GENE | TRANSCRIPT |
|---|---|
| POR | NM_000941.2 |
| POU1F1 | NM_000306.3 |
| PPT1 | NM_000310.3 |
| PRCD | NM_001077620.2 |
| PRDM5 | NM_018699.3 |
| PRF1 | NM_001083116.1 |
| PROP1 | NM_006261.4 |
| PSAP | NM_002778.3 |
| PTPRC* | NM_002838.4 |
| PTS | NM_000317.2 |
| PUS1 | NM_025215.5 |
| PYGM | NM_005609.3 |
| QDPR | NM_000320.2 |
| RAB23 | NM_183227.2 |
| RAG1 | NM_000448.2 |
| RAG2 | NM_000536.3 |
| RAPSN | NM_005055.4 |
| RARS2 | NM_020320.3 |
| RDH12 | NM_152443.2 |
| RLBP1 | NM_000326.4 |
| RMRP | NR_003051.3 |
| RNASEH2A | NM_006397.2 |
| RNASEH2B | NM_024570.3 |
| RNASEH2C | NM_032193.3 |
| RPE65 | NM_000329.2 |
| RPGRIP1L | NM_015272.2 |
| RTEL1 | NM_001283009.1 |
| RXYLT1 | NM_014254.2 |
| RYR1 | NM_000540.2 |
| SACS | NM_014363.5 |
| SAMD9 | NM_017654.3 |
| SAMHD1 | NM_015474.3 |
| SCO2 | NM_005138.2 |
| SEC23B | NM_006363.4 |
| SEPSECS | NM_016955.3 |
| SGCA | NM_000023.2 |
| SGCB | NM_000232.4 |
| SGCD | NM_000337.5 |
| SGCG | NM_000231.2 |

| GENE | TRANSCRIPT |
|---|---|
| SGSH | NM_000199.3 |
| SKIV2L | NM_006929.4 |
| SLC12A1 | NM_000338.2 |
| SLC12A3 | NM_000339.2 |
| SLC12A6 | NM_133647.1 |
| SLC17A5 | NM_012434.4 |
| SLC19A2 | NM_006996.2 |
| SLC19A3 | NM_025243.3 |
| SLC1A4 | NM_003038.4 |
| SLC22A5 | NM_003060.3 |
| SLC25A13 | NM_014251.2 |
| SLC25A15 | NM_014252.3 |
| SLC25A20 | NM_000387.5 |
| SLC26A2 | NM_000112.3 |
| SLC26A3 | NM_000111.2 |
| SLC26A4 | NM_000441.1 |
| SLC27A4 | NM_005094.3 |
| SLC35A3 | NM_012243.2 |
| SLC37A4 | NM_001164277.1 |
| SLC38A8 | NM_001080442.2 |
| SLC39A4 | NM_130849.3 |
| SLC45A2 | NM_016180.4 |
| SLC4A11 | NM_032034.3 |
| SLC5A5 | NM_000453.2 |
| SLC7A7 | NM_001126106.2 |
| SMARCAL1 | NM_014140.3 |
| SMN1* | NM_000344.3 |
| SMPD1 | NM_000543.4 |
| SNAP29 | NM_004782.3 |
| SPG11 | NM_025137.3 |
| SPR | NM_003124.4 |
| SRD5A2 | NM_000348.3 |
| ST3GAL5 | NM_003896.3 |
| STAR | NM_000349.2 |
| STX11 | NM_003764.3 |
| STXBP2 | NM_006949.3 |
| SUMF1 | NM_182760.3 |
| SUOX | NM_000456.2 |
| SURF1 | NM_003172.3 |

| GENE | TRANSCRIPT |
|---|---|
| SYNE4 | NM_001039876.2 |
| TANGO2 | NM_152906.6 |
| TAT | NM_000353.2 |
| TBCD | NM_005993.4 |
| TBCE* | NM_003193.4 |
| TCIRG1 | NM_006019.3 |
| TCN2 | NM_000355.3 |
| TECPR2 | NM_014844.3 |
| TERT | NM_198253.2 |
| TF | NM_001063.3 |
| TFR2 | NM_003227.3 |
| TG* | NM_003235.4 |
| TGM1 | NM_000359.2 |
| TH | NM_199292.2 |
| TK2 | NM_004614.4 |
| TMC1 | NM_138691.2 |
| TMEM216 | NM_001173990.2 |
| TMEM67 | NM_153704.5 |
| TMPRSS3 | NM_024022.2 |
| TPO | NM_000547.5 |
| TPP1 | NM_000391.3 |
| TREX1 | NM_033629.4 |
| TRIM32 | NM_012210.3 |
| TRIM37 | NM_015294.4 |
| TRMU | NM_018006.4 |
| TSEN54 | NM_207346.2 |
| TSFM* | NM_001172696.1 |
| TSHB | NM_000549.4 |
| TSHR | NM_000369.2 |
| TTC37 | NM_014639.3 |
| TTPA | NM_000370.3 |
| TULP1 | NM_003322.4 |
| TYMP | NM_001953.4 |
| TYR* | NM_000372.4 |
| TYRP1 | NM_000550.2 |
| UBR1 | NM_174916.2 |
| UNC13D | NM_199242.2 |
| USH1C* | NM_005709.3 |
| USH2A | NM_206933.2 |

| GENE | TRANSCRIPT |
|---|---|
| VDR | NM_001017535.1 |
| VLDLR | NM_003383.4 |
| VPS11 | NM_021729.5 |
| VPS13A* | NM_033305.2 |
| VPS13B | NM_017890.4 |
| VPS45 | NM_007259.4 |
| VPS53* | NM_001128159.2 |
| VRK1 | NM_003384.2 |
| VSX2 | NM_182894.2 |
| WISP3 | NM_003880.3 |
| WNT10A | NM_025216.2 |
| WRN* | NM_000553.4 |
| XPA | NM_000380.3 |
| XPC | NM_004628.4 |
| ZBTB24 | NM_014797.2 |
| ZFYVE26 | NM_015346.3 |
| ZNF469 | NM_001127464.2 |

## Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated in the Genes Analyzed table. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence, and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Confirmation of the presence and location of reportable variants is performed as needed based on stringent criteria, using one of several validated orthogonal approaches (PubMed ID 30610921). Sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). Confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).

  The following additional analyses are performed if relevant to the requisition. For GBA the reference genome has been modified to mask the sites of polymorphic paralog sequence variants (PSVs) in both the gene and pseudogene. For CYP21A2 and GBA, if one or more reportable variants, gene conversion, or fusion event is identified via our NGS pipeline (see Limitations), these variants are confirmed by PacBio sequencing of an amplicon generated by long-range PCR and subsequent short-range PCR. In some cases, it may not be possible to disambiguate between the gene and pseudogene. For GJB2, the reportable range includes large upstream deletions overlapping GJB6. For HBA1/2, the reference genome has been modified to force some sequencing reads derived from HBA1 to align to HBA2, and variant calling algorithms are modified to support an expectation of 4 alleles in these regions. HBA1/2 copy number calling is performed by a custom hypothesis testing algorithm which generates diplotype calls. If sequence data for a sample does not support a unique high confidence match from among hypotheses tested, that sample is flagged for manual review. Copy number variation is only reported for coding sequence of HBA1 and HBA2 and the HS-40 region. This assay does not distinguish among the -α3.7 subtypes, and all -α3.7 variants are called as HBA1 deletions. This assay may not detect overlapping copy gain and copy loss events when the breakpoints of those events are similar. For FMR1, cytosine-guanine-guanine (CGG) triplet repeats in the 5' untranslated region (5' UTR) of the FMR1 gene are detected by triplet repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Reference ranges: Normal: <45 CGG repeats, intermediate: 45-54 CGG repeats, premutation: 55-200 CGG repeats, full mutation: >200 CGG repeats. For alleles with 55-90 triplet repeats, the region surrounding the FMR1 repeat is amplified by PCR. The PCR amplicons are then processed through PacBio SMRTBell library prep and sequenced using PacBio long read technology. The number of AGG interruptions within the 55-90 triplet repeat is read directly from the resulting DNA sequences.

- This report only includes variants that have a clinically significant association with the conditions tested as of the report date. Variants of uncertain significance, benign variants, and likely benign variants are not included in this report. However, if additional evidence becomes available to indicate that the clinical significance of a variant has changed, Invitae may update this report and provide notification.
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at **http://www.ncbi.nlm.nih.gov/pubmed**.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (**http://exac.broadinstitute.org**), gnomAD (**http://gnomad.broadinstitute.org**), and dbSNP (**http://ncbi.nlm.nih.gov/SNP**).

## Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by

the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

## Limitations

- Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. While this test is intended to reflect the analysis of extracted genomic DNA from a referred patient, in very rare cases the analyzed DNA may not represent that individual's constitutional genome, such as in the case of a circulating hematolymphoid neoplasm, bone marrow transplant, blood transfusion, chimerism, culture artifact or maternal cell contamination. Interpretations are made on the assumption that any clinical information provided, including specimen identity, is accurate.
- ANO10: Sequencing analysis for exons 8 includes only cds +/- 0 bp. ATP8B1: Sequencing analysis for exons 19 includes only cds +/- 10 bp. AIPL1: Sequencing analysis for exons 2 includes only cds +/- 10 bp. GHR: Deletion/duplication and sequencing analysis is not offered for exon 3. TBCE: Sequencing analysis for exons 2 includes only cds +/- 10 bp. CYP21A2: Analysis includes the most common variants (c.92C>T(p.Pro31Leu), c.293-13C>G (intronic), c.332_339delGAGACTAC (p.Gly111Valfs*21), c.518T>A (p.Ile173Asn), c.710T>A (p.Ile237Asn), c.713T>A (p.Val238Glu), c.719T>A (p.Met240Lys), c.844G>T (p.Val282Leu), c.923dupT (p.Leu308Phefs*6), c.955C>T (p.Gln319*), c.1069C>T(p.Arg357Trp), c.1360C>T (p.Pro454Ser) and the 30Kb deletion) as well as select rare HGMD variants only (list available upon request). Full gene duplications are reported only in the presence of a pathogenic variant(s). When a duplication and a pathogenic variant(s) is identified, phase (cis/trans) cannot be determined. Full gene deletion analysis is not offered. Sensitivity to detect these variants, if they result from complex gene conversion/fusion events, may be reduced. TYR: Deletion/duplication and sequencing analysis is not offered for exon 5. PTPRC: Sequencing analysis is not offered for exons 3, 15. ABCC2: Deletion/duplication analysis is not offered for exons 24-25. OTOA: Deletion/duplication and sequencing analysis is not offered for exons 20-28. DUOX2: Deletion/duplication and sequencing analysis is not offered for exons 6-7. TG: Deletion/duplication analysis is not offered for exon 18. Sequencing analysis for exons 44 includes only cds +/- 0 bp. FANCD2: Deletion/duplication analysis is not offered for exons 14-17, 22 and sequencing analysis is not offered for exons 15-17. Sequencing analysis for exons 6, 14, 18, 20, 23, 25, 34 includes only cds +/- 10 bp. FANCL: Sequencing analysis for exons 4, 10 includes only cds +/- 10 bp. ATM: Sequencing analysis for exons 6, 24, 43 includes only cds +/- 10 bp. CFTR: Sequencing analysis for exons 7 includes only cds +/- 10 bp. EYS: Sequencing analysis for exons 30 includes only cds +/- 0 bp. FAH: Deletion/duplication analysis is not offered for exon 14. FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp. GALC: Deletion/duplication analysis is not offered for exon 6. GBA: c.84dupG (p.Leu29Alafs*18), c.115+1G>A (Splice donor), c.222_224delTAC (p.Thr75del), c.475C>T (p.Arg159Trp), c.595_596delCT (p.Leu199Aspfs*62), c.680A>G (p.Asn227Ser), c.721G>A (p.Gly241Arg), c.754T>A (p.Phe252Ile), c.1226A>G (p.Asn409Ser), c.1246G>A (p.Gly416Ser), c.1263_1317del (p.Leu422Profs*4), c.1297G>T (p.Val433Leu), c.1342G>C (p.Asp448His), c.1343A>T (p.Asp448Val), c.1448T>C (p.Leu483Pro), c.1504C>T (p.Arg502Cys), c.1505G>A (p.Arg502His), c.1603C>T (p.Arg535Cys), c.1604G>A (p.Arg535His) variants only. Rarely, sensitivity to detect these variants may be reduced. When sensitivity is reduced, zygosity may be reported as "unknown". GNE: Sequencing analysis for exons 8 includes only cds +/- 10 bp. HBA1/2: This assay is designed to detect deletions and duplications of HBA1 and/or HBA2, resulting from the -alpha20.5, --MED, --SEA, --FIL/--THAI, -alpha3.7, -alpha4.2, anti3.7 and anti4.2. Sensitivity to detect other copy number variants may be reduced. Detection of overlapping deletion and duplication events will be limited to combinations of events with significantly differing boundaries. In addition, deletion of the enhancer element HS-40 and the sequence variant, Constant Spring (NM_000517.4:c.427T>C), can be identified by this assay. HBA2: Sequencing analysis is not offered for exons 1-2. LIFR: Sequencing analysis for exons 3 includes only cds +/- 5 bp. MLC1: Sequencing analysis for exons 11 includes only cds +/- 10 bp. MTHFR: The NM_005957.4:c.665C>T (p.Ala222Val) (aka 677C>T) and c.1286A>C (p.Glu429Ala) (aka 1298A>C) variants are not reported in our primary report. NEB: Deletion/duplication analysis is not offered for exons 82-105. NEB variants in this region with no evidence towards pathogenicity are not included in this report, but are available upon request. OAT: Deletion/duplication analysis is not offered for exon 2. PEX1: Sequencing analysis for exons 16 includes only cds +/- 0 bp. PKHD1: Deletion/duplication analysis is not offered for exon 13. SMN1: Systematic exon numbering is used for all genes, including SMN1, and for this reason the exon typically referred to as exon 7 in the literature (PMID: 8838816) is referred to as exon 8 in this

report. This assay unambiguously detects SMN1 exon 8 copy number. The presence of the g.27134T>G variant (also known as c.*3+80T>G) is reported if SMN1 copy number = 2. SMN1 or SMN2: NM_000344.3:c.*3+80T>G variant only. TSFM: Sequencing analysis is not offered for exon 5. USH1C: Deletion/duplication analysis is not offered for exons 5-6. VPS13A: Deletion/duplication analysis is not offered for exons 2-3, 27-28. VPS53: Sequencing analysis for exons 14 includes only cds +/- 5 bp. AMN: Deletion/duplication analysis is not offered for exon 1. GALE: Sequencing analysis for exons 10 includes only cds +/- 5 bp. DDX11: NM_030653.3:c.1763-1G>C variant only. BBS9: Deletion/duplication analysis is not offered for exon 4. COL11A2: Deletion/duplication analysis is not offered for exon 36. WRN: Deletion/duplication analysis is not offered for exons 10-11. Sequencing analysis for exons 8, 10-11 includes only cds +/- 10 bp.

## This report has been reviewed and approved by:

Mei Zhu, Ph.D., FACMG
Clinical Molecular Geneticist

mz_49e6_pr

PATIENT INFORMATION
**7256,DONOR**

REPORT STATUS **Final**

Nichols Institute, Chantilly

DOB: [redacted] Age: [redacted]
SEX: M

ORDERING PHYSICIAN
[redacted]

CLIENT INFORMATION
[redacted]

SPECIMEN INFORMATION
SPECIMEN: [redacted]
REQUISITION: [redacted]
LAB REF NO: [redacted]

ID: 7256-[redacted]

COLLECTED: 12/19/2023 00:00
RECEIVED: 12/20/2023 16:12
REPORTED: 12/27/2023 19:12

| Test Name | In Range | Out of Range | Reference Range | Lab |
|---|---|---|---|---|
| Hemoglobinopathy Evaluation | | | | AMD |
| Red Blood Cell Count | 5.18 | | 4.20-5.80 Mill/uL | |
| HEMOGLOBIN | 15.3 | | 13.2-17.1 g/dL | |
| Hematocrit | | | | |
| Hematocrit | 45.8 | | 38.5-50.0 % | |
| MCV | 88.4 | | 80.0-100.0 fL | |
| MCH | 29.5 | | 27.0-33.0 pg | |
| RDW | 12.8 | | 11.0-15.0 % | |
| Hemoglobin A | 97.7 | | >96.0 % | |
| Hemoglobin F | 0.0 | | <2.0 % | |
| Hemoglobin A2 (Quant) | 2.3 | | 2.2-3.2 % | |
| Interpretation | | | | |

NORMAL PATTERN

There is a normal pattern of hemoglobins and normal levels of Hb A2 and Hb F are present.
No variant hemoglobins are observed. This is consistent with A/A phenotype.
If iron deficiency coexists with a mild/silent beta thalassemia trait Hb A2 may be in the normal range.
Rare variant hemoglobins have no separation from hemoglobin A by capillary zone electrophoresis (CZE) or high-performance liquid chromatography (HPLC).
If clinically indicated, Thalassemia and Hemoglobinopathy Comprehensive (TC 17365) should be considered.

| | | | | |
|---|---|---|---|---|
| CBC (includes Differential and Platelets) | | | | AMD |
| CBC (includes Differential and Platelets) | | | | |
| White Blood Cell Count | 6.5 | | 3.8-10.8 Thous/uL | |
| Red Blood Cell Count | 5.18 | | 4.20-5.80 Mill/uL | |
| HEMOGLOBIN | 15.3 | | 13.2-17.1 g/dL | |
| Hematocrit | 45.8 | | 38.5-50.0 % | |
| MCV | 88.4 | | 80.0-100.0 fL | |
| MCH | 29.5 | | 27.0-33.0 pg | |
| MCHC | 33.4 | | 32.0-36.0 g/dL | |
| RDW | 12.8 | | 11.0-15.0 % | |
| PLATELET COUNT | 268 | | 140-400 Thous/uL | |
| MPV | 9.8 | | 7.5-12.5 fl | |

PATIENT INFORMATION
**7256,DONOR**

REPORT STATUS **Final**

Nichols Institute, Chantilly

ORDERING PHYSICIAN
[redacted]

DOB: [redacted] Age: [redacted]
SEX: M
ID: 7256-[redacted]

COLLECTED: 12/19/2023 00:00
REPORTED: 12/27/2023 19:12

| Test Name | In Range | Out of Range | Reference Range | Lab |
|---|---|---|---|---|
| CBC (includes Differential and Platelets) (Continued) | | | | |
| Absolute Neutrophils | 3608 | | 1500-7800 cells/uL | |
| Absolute Lymphocytes | 2496 | | 850-3900 cells/uL | |
| Absolute Monocytes | 306 | | 200-950 cells/uL | |
| Absolute Eosinophils | 52 | | 15-500 cells/uL | |
| Absolute Basophils | 39 | | 0-200 cells/uL | |
| Neutrophils | 55.5 | | % | |
| Lymphocytes | 38.4 | | % | |
| Monocytes | 4.70 | | % | |
| Eosinophils | 0.80 | | % | |
| Basophils | 0.60 | | % | |
| Nucleated RBC | 0.00 | | 0 /100 WBC | |
| [redacted] | [redacted] | | [redacted] | [redacted] |
| [redacted] | [redacted] | | [redacted] | [redacted] |
| [redacted] | [redacted] | | [redacted] | [redacted] |
| Chromosome Analysis, Blood | | | | AMD |
| Chromosome Analysis, Blood | | | | |
| Chromosome Analysis, Blood | | | | |

Order ID: [redacted]

Specimen Type: Blood

Clinical Indication: Semen donor

RESULT:
NORMAL MALE KARYOTYPE

INTERPRETATION:
Chromosome analysis revealed normal G-band patterns within the limits of standard cytogenetic analysis.

Please expect the results of any other concurrent study in a separate report.

NOMENCLATURE:
46,XY

ASSAY INFORMATION:
Method: G-Band (Digital Analysis: MetaSystems/Ikaros)
Cells Counted: 20
Band Level: 550
Cells Analyzed: 5
Cells Karyotyped: 3

This test does not address genetic disorders that cannot be detected by standard cytogenetic methods or rare events such as low level mosaicism or subtle rearrangements.

Steven A. Schonberg, Ph.D., FACMG, Technical Director, Cytogenetics

PATIENT INFORMATION
**7256,DONOR**

REPORT STATUS **Final**

Nichols Institute, Chantilly

ORDERING PHYSICIAN [redacted]

DOB: [redacted] Age: [redacted]
SEX: M
ID: 7256-[redacted]

COLLECTED: 12/19/2023 00:00
REPORTED: 12/27/2023 19:12

| Test Name | In Range | Out of Range | Reference Range | Lab |
|---|---|---|---|---|

Chromosome Analysis, Blood (Continued)
Chromosome Analysis, Blood (Continued)
and Genomics, 703-802-7156

Electronic Signature: 12/27/2023 6:26 PM

For additional information, please refer to
http://education.questdiagnostics.com/faq/chromsblood
(This link is being provided for informational/
educational purposes only).

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**Performing Laboratory Information:**

AMD Quest Diagnostics Nichols Institute 14225 Newbrook Drive Chantilly VA 20151 Laboratory Director: Patrick W Mason, MD PhD