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# Genetic Testing Summary

Enclosed are the genetic testing results for

## PC 506-B

No amount of genetic testing can guarantee that a child will not be affected with a genetic condition. Genetic testing can inform you of the likelihood of passing on the genetic conditions that are tested for, but it cannot eliminate the risk of passing on any genetic condition.

The genetic conditions Cryobio tests for are inherited in an autosomal recessive manner. This means that the child would have to inherit a genetic mutation from both the sperm source and the egg source to be affected with the condition. When both the sperm source and the egg source have undergone genetic carrier screening and the test results are negative, the risk of a child being affected with the conditions tested for is significantly reduced, but it cannot be completely eliminated.

All recipients should discuss both or their own risk for passing on genetic conditions and whether would benefit from genetic counseling and testing with their health care provider. Before using a donor that is a carrier for a specific recessive genetic condition or conditions, we strongly recommend that the recipient (or egg source, if different) consider genetic counseling and testing to determine if they are a carrier for the same genetic condition or conditions as the donor.

Screening and testing have changed dramatically over the years, and so the screening and testing done on each donor may very depending on the testing that was in place when he was actively in Cryobio's donor program. Earlier donors may not have had as extensive testing as later donors. Screening and testing may change again in the future, so please review the results each time before ordering as both the testing done and the results may change.

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CARRIER SCREENING REPORT

| Patient | Sample | Referring Doctor |
|---|---|---|
| **Patient Name:** Pc 506-B<br>**Date of Birth:** [redacted]<br>**Reference #:** [redacted]<br>**Indication:** Carrier Testing<br>**Test Type:** Expanded Carrier Screen (283) | **Specimen Type:** Blood<br>**Lab #:** [redacted]<br>**Date Collected:** [redacted]<br>**Date Received:** [redacted]<br>**Final Report:** [redacted] | **David Prescott, M.D.**<br>**Cryobiology, Inc.**<br>**4830-D Knightsbridge Blvd.**<br>**Columbus, OH 43214**<br><br>Fax: **614-451-5284** |

# RESULT SUMMARY

## THIS PATIENT WAS TESTED FOR 283 DISEASES.

**Please see Table 1 for list of diseases tested.**

**POSITIVE for alpha-thalassemia**

One copy of the alpha 3.7 deletion detected

**POSITIVE for biotinidase deficiency**

A heterozygous (one copy) pathogenic variant, c.1330G>C, p.D444H, was detected in the *BTD* gene

**Increased risk of being an *SMN1* silent (2+0) carrier for spinal muscular atrophy**

c.*3+80T>G positive with 2 copies of *SMN1* (see SMA table for modified residual risk)

**NEGATIVE for the remaining diseases**

**Recommendations**

Testing the partner for the above positive disorder(s) and genetic counseling are recommended.

Please note that for female carriers of X-linked diseases, follow-up testing of a male partner is not indicated. In addition, CGG repeat analysis of *FMR1* for fragile X syndrome is not performed on males as repeat expansion of premutation alleles is not expected in the male germline.

Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.

Consideration of residual risk by ethnicity after a negative carrier screen is recommended for the other diseases on the panel, especially in the case of a positive family history for a specific disorder.

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
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**Interpretation for biotinidase deficiency**

A heterozygous (one copy) pathogenic missense variant, c.1330G>C, p.D444H, was detected in the *BTD* gene (NM_000060.3). Please note that this is a mild variant and is not expected to result in a disease phenotype when homozygous, unless present as part of a complex allele. If found in trans with a severe pathogenic variant, the individual is expected to develop partial biotinidase deficiency. When this variant is present in trans with a pathogenic variant, it is considered to be causative for biotinidase deficiency. Therefore, this individual is expected to be at least a carrier for biotinidase deficiency. Heterozygous carriers are not expected to exhibit symptoms of this disease.

**What is biotinidase deficiency?**

Biotinidase deficiency is an autosomal recessive disorder caused by pathogenic variants in the gene *BTD*. This pan-ethnic disorder affects individuals within the first few months of life. Severe forms of the disorder cause children to experience neurological abnormalities such as seizures, hypotonia, developmental delay, and vision problems as well as hearing problems, respiratory problems, and cutaneous abnormalities. While effective treatment is available, symptoms such as vision problems, hearing loss, and developmental delay are irreversible. Several specific variants have been associated with full or partial biotinidase deficiency, and therefore the severity of the disease may be predicted based on the genotype.

This patient was tested for a panel of diseases using a combination of sequencing, targeted genotyping and copy number analysis. Please note that negative results reduce but do not eliminate the possibility that this individual is a carrier for one or more of the disorders tested. Please see Table 1 for a list of genes and diseases tested, and http://go.sema4.com/residualrisk for specific detection rates and residual risk by ethnicity. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate. Only variants determined to be pathogenic or likely pathogenic are reported in this carrier screening test.

## TEST SPECIFIC RESULTS

***Alpha-thalassemia***

**POSITIVE for alpha-thalassemia**
*HBA1* copy number: 2
*HBA2* copy number: 1
One copy of the alpha 3.7 deletion detected
*HBA1* and *HBA2* sequence analysis: No pathogenic or likely pathogenic variants identified
Silent alpha-thalassemia carrier (aa/-a)

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**Genes analyzed:** *HBA1* (NM_000558.4) and *HBA2* (NM_000517.4)
**Inheritance:** Autosomal Recessive

**Recommendations**
Testing of the patient's partner and genetic counseling are recommended.

Individuals of Asian, African, Hispanic and Mediterranean ancestry should also be screened for hemoglobinopathies by CBC and hemoglobin electrophoresis.

**Interpretation**
This patient carries a heterozygous alpha 3.7 deletion, resulting in the loss of one copy of the alpha-globin gene and is therefore a silent carrier of alpha-thalassemia (aa/-a). No pathogenic or likely pathogenic variants were identified by sequence analysis.

Typically, individuals have four functional alpha-globin genes: 2 copies of *HBA1* and 2 copies of *HBA2*, whose expression is regulated by a cis-acting regulatory element HS-40. Alpha-thalassemia carriers have three (silent carrier) or two (carrier of the alpha-thalassemia trait) functional alpha-globin genes with or without a mild phenotype.

**What is alpha-thalassemia?**
Alpha-thalassemia is an autosomal recessive condition that affects the red blood cells. It can affect people of any ethnicity, but is more common in people who can trace their ancestry to Southeast Asia, India, equatorial Africa, the Mediterranean, or the Arabian Peninsula. There are two major forms of alpha-thalassemia:

- Hemoglobin Bart syndrome is caused by a loss of all 4 alpha-globin genes (--/--). It is very severe, and fetuses are either stillborn or die shortly after birth.
- Alpha-thalassemia (also called HbH disease) is caused by a loss of 3 alpha-globin genes (-a/--). This disease results in anemia, an enlarged spleen, and mild jaundice. Most individuals are mildly disabled by this condition. Some people with more severe disease require frequent blood transfusions.

The type of disease as well as the severity of symptoms can be predicted based on the genetic variants detected. Carriers may have mild anemia.

## ***Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency)***

**NEGATIVE for congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)**
*CYP21A2* copy number: 2
No pathogenic copy number variants detected
No pathogenic sequence variants detected in *CYP21A2*
Reduced risk of being a congenital adrenal hyperplasia carrier

**Genes analyzed:** *CYP21A2* (NM_000500.6)

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
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**Inheritance:** Autosomal Recessive

**Recommendations**

Consideration of residual risk by ethnicity (see below) after a negative carrier screen is recommended, especially in the case of a positive family history of congenital adrenal hyperplasia.

**Interpretation**

This individual was negative for all pathogenic *CYP21A2* copy number variants that were tested, and no pathogenic or likely pathogenic variants were identified by sequence analysis. These negative results reduce but do not eliminate the possibility that this individual is a carrier. See *Table of Residual Risks Based on Ethnicity*. With individuals of mixed ethnicity, it is recommended to use the highest residual risk estimate.

**Table of Residual Risk Based On Ethnicity - Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency**

| Ethnicity | Carrier Frequency | Detection Rate | Residual Risk |
|---|---|---|---|
| Ashkenazi Jewish | 1 in 40 | >95% | 1 in 780 |
| Caucasian | 1 in 67 | >95% | 1 in 1300 |
| Worldwide | 1 in 60 | >95% | 1 in 1200 |

**Table of Residual Risk Based On Ethnicity - Non-Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency**

| Ethnicity | Carrier Frequency | Detection Rate | Residual Risk |
|---|---|---|---|
| Ashkenazi Jewish | 1 in 7 | >95% | 1 in 120 |
| Caucasian | 1 in 11 | >95% | 1 in 200 |
| Worldwide | 1 in 16 | >95% | 1 in 300 |

***Fragile X syndrome***

Fragile X CGG triplet repeat expansion testing was not performed at this time, as the patient has either been previously tested or is a male. Sequencing of the *FMR1* gene by next generation sequencing did not identify any clinically significant variants.

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## ***Spinal Muscular Atrophy***

*SMN1* Copy Number: 2
*SMN2* Copy Number: 1
c.*3+80T>G: Detected

**Negative copy number result**
**Increased risk of being an *SMN1* silent (2+0) carrier (see *SMA Table*)**

**Genes analyzed**: *SMN1* (NM_000344.3) and *SMN2* (NM_017411.3)
**Inheritance:** Autosomal Recessive

**Recommendations**
Testing the partner for this condition and genetic counseling are recommended.

**Interpretation**
This patient is negative for loss of *SMN1* copy number. Complete loss of *SMN1* is causative in spinal muscular atrophy (SMA). Two copies of *SMN1* were detected in this individual, which is considered a negative copy number result. However, parallel testing to assess the presence of an *SMN1* duplication allele was also performed to detect a single nucleotide polymorphism (SNP), c.*3+80T>G, in intron 7 of the *SMN1* gene. This individual was found to be positive for this change and is therefore, at an increased risk of being a silent (2+0) carrier. See *SMA Table* for residual risk estimates based on ethnicity.

**SMA Table: Carrier detection and residual risk estimates before and after testing for c.*3+80T>G**

| Ethnicity | Carrier Frequency | Detection rate | Residual risk after negative result* | Detection rate with *SMN1* c.*3+80T>G | Residual risk c.*3+80T>G negative | Residual risk c.*3+80T>G positive |
|---|---|---|---|---|---|---|
| African American | 1 in 85 | 71% | 1 in 160 | 91% | 1 in 455 | 1 in 49 |
| Ashkenazi Jewish | 1 in 76 | 90% | 1 in 672 | 93% | 1 in 978 | 1 in 10 |
| East Asian | 1 in 53 | 94% | 1 in 864 | 95% | 1 in 901 | 1 in 12 |
| Caucasian | 1 in 48 | 95% | 1 in 803 | 95% | 1 in 894 | 1 in 23 |
| Latino | 1 in 63 | 91% | 1 in 609 | 94% | 1 in 930 | 1 in 47 |
| South Asian | 1 in 103 | 87% | 1 in 637 | 87% | 1 in 637 | 1 in 608 |
| Sephardic Jewish | 1 in 34 | 96% | 1 in 696 | 97% | 1 in 884 | 1 in 12 |

*Residual risk with two copies *SMN1* detected using dosage sensitive methods. The presence of three or more copies of *SMN1* reduces the risk of being an *SMN1* carrier between 5 - 10 fold, depending on ethnicity.
*FOR INDIVIDUALS WITH MIXED ETHNICITY, USE HIGHEST RESIDUAL RISK ESTIMATE*
^ Parental follow-up will be requested for confirmation

**What is spinal muscular atrophy?**

Spinal muscular atrophy (SMA) is a pan-ethnic, autosomal recessive disease caused by loss of function of the *SMN1* gene. In over 95% of cases, patients are missing both copies of the *SMN1* gene. The disease is characterized by the degeneration of alpha motor neurons of the spinal cord anterior horn cells, leading to progressive symmetric weakness, atrophy of the proximal voluntary muscles and early death. Age of onset can be anywhere on a continuum from the prenatal period to adulthood.

- SMA 0 represents the most severe form. Infants are born with severe hypotonia and joint contractures; no

motor milestones are achieved and patients die before 6 months of age.
• SMA I has an age of onset in the first six months of life. These cases are associated with death usually by age 2 and the lack of development of motor skills.
• SMA II has an age of onset between 3 and 15 months; patients may be able to sit independently. Intelligence is not affected. Life expectancy may vary from early childhood to early adulthood.
• SMA III has an age of onset after 18 months of age and as late as adolescence; patients may learn to stand and to walk short distances. These patients may have a normal lifespan.
• SMA IV is an adult-onset disorder of muscle weakness; life span is not shortened.

Most patients, regardless of the severity of disease, have a deletion of both *SMN1* copies. Patients with later-onset disease usually have three or more copies of *SMN2*, which encodes a small amount of residual protein and lessens the severity of the symptoms. However, other factors besides *SMN2* copy number may affect the phenotype, and therefore the severity of the disease may not be able to be accurately predicted in all patients based on genotype.

## ***Tay-Sachs Disease Enzyme Analysis***

**Results**: **Non-carrier**

| Specimen | Hexosaminidase Activity | Hex A% | Non-Carrier Range | Comment |
|---|---|---|---|---|
| Tay-Sachs WBC | 928 nmol/hr/mg | 62.0 | 55.0 - 72.0 | Non-Carrier |
| Tay-Sachs Plasma | 237 nmol/hr/ml | 71.9 | 58.0 - 72.0 | Non-Carrier |

**Expected Carrier Ranges:**
Hex A% <54% (Serum/Plasma), Hex A%<50% (WBC)

**Interpretation:**

The test was performed in the patient's plasma and white blood cells (WBC). The Hex A% activities are both within the non-carrier range. These findings are consistent with the patient being a **non-carrier** for Tay-Sachs disease.

This case has been reviewed and electronically signed by Wanqiong Qiao, Ph.D., Assistant Laboratory Director

Laboratory Medical Consultant: George A. Diaz, M.D., Ph.D.

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
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## Test Methods and Comments

Genomic DNA isolated from this patient was analyzed by one or more of the following methodologies, as applicable:

**Fragile X CGG Repeat Analysis (Analytical Detection Rate >99%)**
PCR amplification using Asuragen, Inc. AmplideX® *FMR1* PCR reagents followed by capillary electrophoresis for allele sizing was performed. Samples positive for *FMR1* CGG repeats in the premutation and full mutation size range were further analyzed by Southern blot analysis to assess the size and methylation status of the *FMR1* CGG repeat.

**Genotyping (Analytical Detection Rate >99%)**
Multiplex PCR amplification and allele specific primer extension analyses using the MassARRAY® System were used to identify variants that are complex in nature or are present in low copy repeats. Rare sequence variants may interfere with assay performance.

**Multiplex Ligation-Dependent Probe Amplification (MLPA) (Analytical Detection Rate >99%)**
MLPA® probe sets and reagents from MRC-Holland were used for copy number analysis of specific targets versus known control samples. False positive or negative results may occur due to rare sequence variants in target regions detected by MLPA probes. Analytical sensitivity and specificity of the MLPA method are both 99%.

For alpha thalassemia, the copy numbers of the *HBA1* and *HBA2* genes were analyzed. Alpha-globin gene deletions, triplications, and the Constant Spring (CS) mutation are assessed. This test is expected to detect approximately 90% of all alpha-thalassemia mutations, varying by ethnicity. Carriers of alpha-thalassemia with three or more *HBA* copies on one chromosome, and one or no copies on the other chromosome, may not be detected. With the exception of triplications, other benign alpha-globin gene polymorphisms will not be reported. Analyses of *HBA1* and *HBA2* are performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For Duchenne muscular dystrophy, the copy numbers of all *DMD* exons were analyzed. Potentially pathogenic single exon deletions and duplications are confirmed by a second method. Analysis of *DMD* is performed in association with sequencing of the coding regions.

For congenital adrenal hyperplasia, the copy number of the *CYP21A2* gene was analyzed. This analysis can detect large deletions due to unequal meiotic crossing-over between *CYP21A2* and the pseudogene *CYP21A1P*. These 30-kb deletions make up approximately 20% of *CYP21A2* pathogenic alleles. This test may also identify certain point mutations in *CYP21A2* caused by gene conversion events between *CYP21A2* and *CYP21A1P*. Some carriers may not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *CYP21A2* gene on one chromosome and loss of *CYP21A2* (deletion) on the other chromosome. Analysis of *CYP21A2* is performed in association with long-range PCR of the coding regions followed by short-read sequencing.

For spinal muscular atrophy (SMA), the copy numbers of the *SMN1* and *SMN2* genes were analyzed. The individual dosage of exons 7 and 8 as well as the combined dosage of exons 1, 4, 6 and 8 of *SMN1* and *SMN2* were assessed. Copy number gains and losses can be detected with this assay. Depending on ethnicity, 6 - 29 % of carriers will not be identified by dosage sensitive methods as this testing cannot detect individuals with two copies (duplication) of the *SMN1* gene on one chromosome and loss of *SMN1* (deletion) on the other chromosome (silent 2+0 carrier) or individuals that carry an intragenic mutation in *SMN1*. Please also note that 2% of individuals with SMA have an *SMN1* mutation that occurred *de novo*. Typically in these cases, only one parent is an SMA carrier.

The presence of the c.*3+80T>G (chr5:70,247,901T>G) variant allele in an individual with Ashkenazi Jewish or Asian ancestry is typically indicative of a duplication of *SMN1*. When present in an Ashkenazi Jewish or Asian individual with two copies of *SMN1*, c.*3+80T>G is likely indicative of a silent (2+0) carrier. In individuals with two copies of *SMN1* with African American, Hispanic or Caucasian ancestry, the presence or absence of c.*3+80T>G significantly increases or decreases, respectively, the likelihood of being a silent 2+0 silent carrier.

Pathogenic or likely pathogenic sequence variants in exon 7 may be detected during testing for the c.*3+80T>G variant allele; these will be reported if confirmed to be located in SMN1 using locus-specific Sanger primers

MLPA for Gaucher disease (*GBA*), cystic fibrosis (*CFTR*), and non-syndromic hearing loss (*GJB2/GJB6*) will only be performed if indicated for confirmation of detected CNVs. If *GBA* analysis was performed, the copy numbers of exons 1, 3, 4, and 6 - 10 of the *GBA* gene (of 11 exons total) were analyzed. If *CFTR* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of the two *GJB2* exons were analyzed, as well as the presence or absence of the two upstream deletions of the *GJB2* regulatory region, del(*GJB6*-D13S1830) and del(*GJB6*-D13S1854).

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**Next Generation Sequencing (NGS) (Analytical Detection Rate >95%)**
NGS was performed on a panel of genes for the purpose of identifying pathogenic or likely pathogenic variants.

Agilent SureSelect™QXT technology was used with a custom capture library to target the exonic regions and intron/exon splice junctions of the relevant genes, as well as a number of UTR, intronic or promoter regions that contain previously reported mutations. Samples were pooled and sequenced on the Illumina HiSeq 2500 platform in the Rapid Run mode or the Illumina NovaSeq platform in the Xp workflow, using 100 bp paired-end reads. The sequencing data was analyzed using a custom bioinformatics algorithm designed and validated in house.

The coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage (minimum of 20X) and data quality threshold values. Most exons not meeting a minimum of >20X read depth across the exon are further analyzed by Sanger sequencing. Please note that several genomic regions present difficulties in mapping or obtaining read depth >20X. The exons contained within these regions are noted within Table 1 (as "Exceptions") and will not be reflexed to Sanger sequencing if the mapping quality or coverage is poor. Any variants identified during testing in these regions are confirmed by a second method and reported if determined to be pathogenic or likely pathogenic. However, as there is a possibility of false negative results within these regions, detection rates and residual risks for these genes have been calculated with the presumption that variants in these exons will not be detected, unless included in the MassARRAY® genotyping platform.

This test will detect variants within the exons and the intron-exon boundaries of the target regions. Variants outside these regions may not be detected, including, but not limited to, UTRs, promoters, and deep intronic areas, or regions that fall into the Exceptions mentioned above. This technology may not detect all small insertion/deletions and is not diagnostic for repeat expansions and structural genomic variation. In addition, a mutation(s) in a gene not included on the panel could be present in this patient.

Variant interpretation and classification was performed based on the American College of Medical Genetics Standards and Guidelines for the Interpretation of Sequence Variants (Richards et al, 2015). All potentially pathogenic variants may be confirmed by either a specific genotyping assay or Sanger sequencing, if indicated. Any benign variants, likely benign variants or variants of uncertain significance identified during this analysis will not be reported.

**Copy Number Variant Analysis (Analytical Detection Rate >95%)**
Large duplications and deletions were called from the relative read depths on an exon-by-exon basis using a custom exome hidden Markov model (XHMM) algorithm. Deletions or duplications determined to be pathogenic or likely pathogenic were confirmed by either a custom arrayCGH platform, quantitative PCR, or MLPA (depending on CNV size and gene content). While this algorithm is designed to pick up deletions and duplications of 2 or more exons in length, potentially pathogenic single-exon CNVs will be confirmed and reported, if detected.

**Exon Array (Confirmation method) (Accuracy >99%)**
The customized oligonucleotide microarray (Oxford Gene Technology) is a highly-targeted exon-focused array capable of detecting medically relevant microdeletions and microduplications at a much higher resolution than traditional aCGH methods. Each array matrix has approximately 180,000 60-mer oligonucleotide probes that cover the entire genome. This platform is designed based on human genome NCBI Build 37 (hg19) and the CGH probes are enriched to target the exonic regions of the genes in this panel.

**Quantitative PCR (Confirmation method) (Accuracy >99%)**
The relative quantification PCR is utilized on a Roche Universal Library Probe (UPL) system, which relates the PCR signal of the target region in one group to another. To test for genomic imbalances, both sample DNA and reference DNA is amplified with primer/probe sets that specific to the target region and a control region with known genomic copy number. Relative genomic copy numbers are calculated based on the standard ΔΔCt formula.

**Long-Range PCR (Analytical Detection Rate >99%)**
Long-range PCR was performed to generate locus-specific amplicons for *CYP21A2*, *HBA1* and *HBA2* and *GBA*. The PCR products were then prepared for short-read NGS sequencing and sequenced. Sequenced reads were mapped back to the original genomic locus and run through the bioinformatics pipeline. If indicated, copy number from MLPA was correlated with the sequencing output to analyze the results. For *CYP21A2*, a certain percentage of healthy individuals carry a duplication of the *CYP21A2* gene, which has no clinical consequences. In cases where two copies of a gene are located on the same chromosome in tandem, only the second copy will be amplified and assessed for potentially pathogenic variants, due to size limitations of the PCR reaction. However, because these alleles contain at least two copies of the *CYP21A2* gene in tandem, it is expected that this patient has at least one functional gene in the tandem allele and this patient is therefore less likely to be a carrier. When an individual carries both a duplication allele and a pathogenic variant, or multiple pathogenic variants, the current analysis may not be able to

determine the phase (cis/trans configuration) of the *CYP21A2* alleles identified. Family studies may be required in certain scenarios where phasing is required to determine the carrier status.

**Residual Risk Calculations**
Carrier frequencies and detection rates for each ethnicity were calculated through the combination of internal curations of >28,000 variants and genomic frequency data from >138,000 individuals across seven ethnic groups in the gnomAD database. Additional variants in HGMD and novel deleterious variants were also incorporated into the calculation. Residual risk values are calculated using a Bayesian analysis combining the *a priori* risk of being a pathogenic mutation carrier (carrier frequency) and the detection rate. They are provided only as a guide for assessing approximate risk given a negative result, and values will vary based on the exact ethnic background of an individual. This report does not represent medical advice but should be interpreted by a genetic counselor, medical geneticist or physician skilled in genetic result interpretation and the relevant medical literature.

**Sanger Sequencing (Confirmation method) (Accuracy >99%)**
Sanger sequencing, as indicated, was performed using BigDye Terminator chemistry with the ABI 3730 DNA analyzer with target specific amplicons. It also may be used to supplement specific guaranteed target regions that fail NGS sequencing due to poor quality or low depth of coverage (<20 reads) or as a confirmatory method for NGS positive results. False negative results may occur if rare variants interfere with amplification or annealing.

**Tay-Sachs Disease (TSD) Enzyme Analysis (Analytical Detection Rate ≥98%)**
Hexosaminidase activity and Hex A% activity were measured by a standard heat-inactivation, fluorometric method using artificial 4-MU-β-N-acetyl glucosaminide (4-MUG) substrate. This assay is highly sensitive and accurate in detecting Tay-Sachs carriers and individuals affected with TSD. Normal ranges of Hex A% activity are 55.0-72.0 for white blood cells and 58.0-72.0 for plasma. It is estimated that less than 0.5% of Tay-Sachs carriers have non-carrier levels of percent Hex A activity, and therefore may not be identified by this assay. In addition, this assay may detect individuals that are carriers of or are affected with Sandhoff disease. False positive results may occur if benign variants, such as pseudodeficiency alleles, interfere with the enzymatic assay. False negative results may occur if both *HEXA* and *HEXB* pathogenic or pseudodeficiency variants are present in the same individual.

Please note these tests were developed and their performance characteristics were determined by Mount Sinai Genomics, Inc. They have not been cleared or approved by the FDA. These analyses generally provide highly accurate information regarding the patient's carrier or affected status. Despite this high level of accuracy, it should be kept in mind that there are many potential sources of diagnostic error, including misidentification of samples, polymorphisms, or other rare genetic variants that interfere with analysis. Families should understand that rare diagnostic errors may occur for these reasons.

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Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015 May;17(5):405-24

Additional disease-specific references available upon request.

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
|---|---|---|---|---|---|

## Table 1. List of genes and diseases tested.

**Please see http://go.sema4.com/residualrisk for specific detection rates and residual risk by ethnicity.**

| Gene | Disease |
|---|---|
| ***ACADM*** | Medium Chain Acyl-CoA Dehydrogenase Deficiency |
| ***ABCB11*** | Progressive Familial Intrahepatic Cholestasis, Type 2 |
| ***ABCC8*** | Familial Hyperinsulinism (ABCC8-Related) |
| ***ABCD1*** | Adrenoleukodystrophy, X-Linked |
| ***ACAD9*** | Mitochondrial Complex I Deficiency (ACAD9-Related) |
| ***ACADVL*** | Very Long Chain Acyl-CoA Dehydrogenase Deficiency |
| ***ACAT1*** | Beta-Ketothiolase Deficiency |
| ***ACOX1*** | Acyl-CoA Oxidase I Deficiency |
| ***ACSF3*** | Combined Malonic and Methylmalonic Aciduria |
| ***ADA*** | Adenosine Deaminase Deficiency |
| ***ADAMTS2*** | Ehlers-Danlos Syndrome, Type VIIC |
| ***AGA*** | Aspartylglycosaminuria |
| ***AGL*** | Glycogen Storage Disease, Type III |
| ***AGPS*** | Rhizomelic Chondrodysplasia Punctata, Type 3 |
| ***AGXT*** | Primary Hyperoxaluria, Type 1 |
| ***AIRE*** | Polyglandular Autoimmune Syndrome, Type 1 |
| ***ALDH3A2*** | Sjogren-Larsson Syndrome |
| ***ALDOB*** | Hereditary Fructose Intolerance |
| ***ALG6*** | Congenital Disorder of Glycosylation, Type Ic |
| ***ALMS1*** | Alstrom Syndrome |
| ***ALPL*** | Hypophosphatasia |
| ***AMT*** | Glycine Encephalopathy (AMT-Related) |
| ***AQP2*** | Nephrogenic Diabetes Insipidus, Type II |
| ***ARSA*** | Metachromatic Leukodystrophy |
| ***ARSB*** | Mucopolysaccharidosis type VI |
| ***ASL*** | Argininosuccinic Aciduria |
| ***ASNS*** | Asparagine Synthetase Deficiency |
| ***ASPA*** | Canavan Disease |
| ***ASS1*** | Citrullinemia, Type 1 |
| ***ATM*** | Ataxia-Telangiectasia |
| ***ATP6V1B1*** | Renal Tubular Acidosis and Deafness |
| ***ATP7A*** | Menkes Disease |
| ***ATP7B*** | Wilson Disease |
| ***ATRX*** | Alpha-Thalassemia Mental Retardation Syndrome |
| ***BBS1*** | Bardet-Biedl Syndrome (BBS1-Related) |
| ***BBS10*** | Bardet-Biedl Syndrome (BBS10-Related) |
| ***BBS12*** | Bardet-Biedl Syndrome (BBS12-Related) |
| ***BBS2*** | Bardet-Biedl Syndrome (BBS2-Related) |
| ***BCKDHA*** | Maple Syrup Urine Disease, Type 1a |
| ***BCKDHB*** | Maple Syrup Urine Disease, Type 1b |
| ***BCS1L*** | GRACILE Syndrome and Other BCS1L-Related Disorders |
| ***BLM*** | Bloom Syndrome |
| ***BSND*** | Bartter Syndrome, Type 4A |
| ***BTD*** | Biotinidase Deficiency |
| ***CAPN3*** | Limb-Girdle Muscular Dystrophy, Type 2A |
| ***CBS*** | Homocystinuria (CBS-Related) |
| ***CDH23*** | Usher Syndrome, Type ID |
| ***CEP290*** | Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies |
| ***CERKL*** | Retinitis Pigmentosa 26 |

| Gene | Disease |
|---|---|
| ***CFTR*** | Cystic Fibrosis |
| ***CHM*** | Choroideremia |
| ***CHRNE*** | Congenital Myasthenic Syndrome (CHRNE-Related) |
| ***CIITA*** | Bare Lymphocyte Syndrome, Type II |
| ***CLN3*** | Neuronal Ceroid-Lipofuscinosis (CLN3-Related) |
| ***CLN5*** | Neuronal Ceroid-Lipofuscinosis (CLN5-Related) |
| ***CLN6*** | Neuronal Ceroid-Lipofuscinosis (CLN6-Related) |
| ***CLN8*** | Neuronal Ceroid-Lipofuscinosis (CLN8-Related) |
| ***CLRN1*** | Usher Syndrome, Type III |
| ***CNGB3*** | Achromatopsia |
| ***COL27A1*** | Steel Syndrome |
| ***COL4A3*** | Alport Syndrome (COL4A3-Related) |
| ***COL4A4*** | Alport Syndrome (COL4A4-Related) |
| ***COL4A5*** | Alport Syndrome (COL4A5-Related) |
| ***COL7A1*** | Dystrophic Epidermolysis Bullosa |
| ***CPS1*** | Carbamoylphosphate Synthetase I Deficiency |
| ***CPT1A*** | Carnitine Palmitoyltransferase IA Deficiency |
| ***CPT2*** | Carnitine Palmitoyltransferase II Deficiency |
| ***CRB1*** | Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy |
| ***CTNS*** | Cystinosis |
| ***CTSK*** | Pycnodysostosis |
| ***CYBA*** | Chronic Granulomatous Disease (CYBA-related) |
| ***CYBB*** | Chronic Granulomatous Disease (CYBB-related) |
| ***CYP11B2*** | Corticosterone Methyloxidase Deficiency |
| ***CYP17A1*** | Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency |
| ***CYP21A2*** | Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency |
| ***CYP19A1*** | Aromatase Deficiency |
| ***CYP27A1*** | Cerebrotendinous Xanthomatosis |
| ***DCLRE1C*** | Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type |
| ***DHCR7*** | Smith-Lemli-Opitz Syndrome |
| ***DHDDS*** | Retinitis Pigmentosa 59 |
| ***DLD*** | Lipoamide Dehydrogenase Deficiency |
| ***DMD*** | Duchenne Muscular Dystrophy / Becker Muscular Dystrophy |
| ***DNAH5*** | Primary Ciliary Dyskinesia (DNAH5-Related) |
| ***DNAI1*** | Primary Ciliary Dyskinesia (DNAI1-Related) |
| ***DNAI2*** | Primary Ciliary Dyskinesia (DNAI2-related) |
| ***DYSF*** | Limb-Girdle Muscular Dystrophy, Type 2B |
| ***EDA*** | Hypohidrotic Ectodermal Dysplasia 1 |
| ***EIF2B5*** | Leukoencephalopathy with Vanishing White Matter |
| ***EMD*** | Emery-Dreifuss Myopathy 1 |
| ***ESCO2*** | Roberts Syndrome |
| ***ETFA*** | Glutaric Acidemia, Type IIa |
| ***ETFDH*** | Glutaric Acidemia, Type IIc |
| ***ETHE1*** | Ethylmalonic Encephalopathy |
| ***EVC*** | Ellis-van Creveld Syndrome (EVC-Related) |
| ***EYS*** | Retinitis Pigmentosa 25 |
| ***F11*** | Factor XI Deficiency |
| ***F9*** | Factor IX Deficiency |
| ***FAH*** | Tyrosinemia, Type I |

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
|---|---|---|---|---|---|

| Gene | Disease |
|---|---|
| ***FAM161A*** | Retinitis Pigmentosa 28 |
| ***FANCA*** | Fanconi Anemia, Group A |
| ***FANCC*** | Fanconi Anemia, Group C |
| ***FANCG*** | Fanconi Anemia, Group G |
| ***FH*** | Fumarase Deficiency |
| ***FKRP*** | Limb-Girdle Muscular Dystrophy, Type 2I |
| ***FKTN*** | Walker-Warburg Syndrome and Other FKTN-Related Dystrophies |
| ***FMR1*** | Fragile X Syndrome |
| ***G6PC*** | Glycogen Storage Disease, Type Ia |
| ***GAA*** | Glycogen Storage Disease, Type II |
| ***GALC*** | Krabbe Disease |
| ***GALK1*** | Galactokinase Deficiency |
| ***GALT*** | Galactosemia |
| ***GAMT*** | Cerebral Creatine Deficiency Syndrome 2 |
| ***GBA*** | Gaucher Disease |
| ***GBE1*** | Glycogen Storage Disease, Type IV / Adult Polyglucosan Body Disease |
| ***GCDH*** | Glutaric Acidemia, Type I |
| ***GFM1*** | Combined Oxidative Phosphorylation Deficiency 1 |
| ***GJB1*** | Charcot-Marie-Tooth Disease, X-Linked |
| ***GJB2†*** | Non-Syndromic Hearing Loss (GJB2-Related) |
| ***GLA*** | Fabry Disease |
| ***GLB1*** | Mucopolysaccharidosis Type IVb / GM1 Gangliosidosis |
| ***GLDC*** | Glycine Encephalopathy (GLDC-Related) |
| ***GLE1*** | Lethal Congenital Contracture Syndrome 1 / Lethal Arthrogryposis with Anterior Horn Cell Disease |
| ***GNE*** | Inclusion Body Myopathy 2 |
| ***GNPTAB*** | Mucolipidosis II / IIIA |
| ***GNPTG*** | Mucolipidosis III Gamma |
| ***GNS*** | Mucopolysaccharidosis Type IIID |
| ***GP1BA*** | Bernard-Soulier Syndrome, Type A1 |
| ***GP9*** | Bernard-Soulier Syndrome, Type C |
| ***GPR56*** | Bilateral Frontoparietal Polymicrogyria |
| ***GRHPR*** | Primary Hyperoxaluria, Type 2 |
| ***HADHA*** | Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency |
| ***HAX1*** | Congenital Neutropenia (HAX1-Related) |
| ***HBA1/HBA2*** | Alpha-Thalassemia |
| ***HBB*** | Beta-Globin-Related Hemoglobinopathies |
| ***HEXA*** | Tay-Sachs Disease |
| ***HEXB*** | Sandhoff Disease |
| ***HFE2*** | Hemochromatosis, Type 2A |
| ***HGSNAT*** | Mucopolysaccharidosis Type IIIC |
| ***HLCS*** | Holocarboxylase Synthetase Deficiency |
| ***HMGCL*** | HMG-CoA Lyase Deficiency |
| ***HOGA1*** | Primary Hyperoxaluria, Type 3 |
| ***HPS1*** | Hermansky-Pudlak Syndrome, Type 1 |
| ***HPS3*** | Hermansky-Pudlak Syndrome, Type 3 |
| ***HSD17B4*** | D-Bifunctional Protein Deficiency |
| ***HSD3B2*** | 3-Beta-Hydroxysteroid Dehydrogenase Type II Deficiency |
| ***HYAL1*** | Mucopolysaccharidosis type IX |
| ***HYLS1*** | Hydrolethalus Syndrome |
| ***IDS*** | Mucopolysaccharidosis Type II |

| Gene | Disease |
|---|---|
| ***IDUA*** | Mucopolysaccharidosis Type I |
| ***IKBKAP*** | Familial Dysautonomia |
| ***IL2RG*** | X-Linked Severe Combined Immunodeficiency |
| ***IVD*** | Isovaleric Acidemia |
| ***KCNJ11*** | Familial Hyperinsulinism (KCNJ11-Related) |
| ***LAMA3*** | Junctional Epidermolysis Bullosa (LAMA3-Related) |
| ***LAMB3*** | Junctional Epidermolysis Bullosa (LAMB3-Related) |
| ***LAMC2*** | Junctional Epidermolysis Bullosa (LAMC2-Related) |
| ***LCA5*** | Leber Congenital Amaurosis 5 |
| ***LDLR*** | Familial Hypercholesterolemia |
| ***LDLRAP1*** | Familial Autosomal Recessive Hypercholesterolemia |
| ***LHX3*** | Combined Pituitary Hormone Deficiency 3 |
| ***LIFR*** | Stuve-Wiedemann Syndrome |
| ***LIPA*** | Wolman Disease / Cholesteryl Ester Storage Disease |
| ***LOXHD1*** | Deafness, Autosomal Recessive 77 |
| ***LPL*** | Lipoprotein Lipase Deficiency |
| ***LRPPRC*** | Leigh Syndrome, French-Canadian Type |
| ***MAN2B1*** | Alpha-Mannosidosis |
| ***MCCC1*** | 3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC1-Related) |
| ***MCCC2*** | 3-Methylcrotonyl-CoA Carboxylase Deficiency (MCCC2-Related) |
| ***MCOLN1*** | Mucolipidosis IV |
| ***MED17*** | Infantile Cerebral and Cerebellar Atrophy |
| ***MEFV*** | Familial Mediterranean Fever |
| ***MESP2*** | Spondylothoracic Dysostosis |
| ***MFSD8*** | Neuronal Ceroid-Lipofuscinosis (MFSD8-Related) |
| ***MKS1*** | Meckel syndrome 1 / Bardet-Biedl Syndrome 13 |
| ***MLC1*** | Megalencephalic Leukoencephalopathy with Subcortical Cysts |
| ***MMAA*** | Methylmalonic Acidemia (MMAA-Related) |
| ***MMAB*** | Methylmalonic Acidemia (MMAB-Related) |
| ***MMACHC*** | Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type |
| ***MMADHC*** | Methylmalonic Aciduria and Homocystinuria, Cobalamin D Type |
| ***MPI*** | Congenital Disorder of Glycosylation, Type Ib |
| ***MPL*** | Congenital Amegakaryocytic Thrombocytopenia |
| ***MPV17*** | Mitochondrial DNA Depletion Syndrome 6 / Navajo Neurohepatopathy |
| ***MTHFR*** | Homocystinuria due to MTHFR Deficiency |
| ***MTM1*** | Myotubular Myopathy 1 |
| ***MTRR*** | Homocystinuria, cblE Type |
| ***MTTP*** | Abetalipoproteinemia |
| ***MUT*** | Methylmalonic Acidemia (MUT-Related) |
| ***MYO7A*** | Usher Syndrome, Type IB |
| ***NAGLU*** | Mucopolysaccharidosis Type IIIB |
| ***NAGS*** | N-Acetylglutamate Synthase Deficiency |
| ***NBN*** | Nijmegen Breakage Syndrome |
| ***NDRG1*** | Charcot-Marie-Tooth Disease, Type 4D |
| ***NDUFAF5*** | Mitochondrial Complex I Deficiency (NDUFAF5-Related) |
| ***NDUFS6*** | Mitochondrial Complex I Deficiency (NDUFS6-Related) |
| ***NEB*** | Nemaline Myopathy 2 |
| ***NPC1*** | Niemann-Pick Disease, Type C (NPC1-Related) |
| ***NPC2*** | Niemann-Pick Disease, Type C (NPC2-Related) |
| ***NPHS1*** | Nephrotic Syndrome (NPHS1-Related) / Congenital Finnish Nephrosis |

| Patient: | Pc 506-B | DOB: | [redacted] | Lab #: | [redacted] |
|---|---|---|---|---|---|

| Gene | Disease |
|---|---|
| ***NPHS2*** | Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome |
| ***NR2E3*** | Enhanced S-Cone Syndrome |
| ***NTRK1*** | Congenital Insensitivity to Pain with Anhidrosis |
| ***OAT*** | Ornithine Aminotransferase Deficiency |
| ***OPA3*** | 3-Methylglutaconic Aciduria, Type III |
| ***OTC*** | Ornithine Transcarbomylase Deficiency |
| ***PAH*** | Phenylalanine Hydroxylase Deficiency |
| ***PCCA*** | Propionic Acidemia (PCCA-Related) |
| ***PCCB*** | Propionic Acidemia (PCCB-Related) |
| ***PCDH15*** | Usher Syndrome, Type IF |
| ***PDHA1*** | Pyruvate Dehydrogenase E1-Alpha Deficiency |
| ***PDHB*** | Pyruvate Dehydrogenase E1-Beta Deficiency |
| ***PEX1*** | Zellweger Syndrome Spectrum (PEX1-Related) |
| ***PEX10*** | Zellweger Syndrome Spectrum (PEX10-Related) |
| ***PEX2*** | Zellweger Syndrome Spectrum (PEX2-Related) |
| ***PEX6*** | Zellweger Syndrome Spectrum (PEX6-Related) |
| ***PEX7*** | Rhizomelic Chondrodysplasia Punctata, Type 1 |
| ***PFKM*** | Glycogen Storage Disease, Type VII |
| ***PHGDH*** | 3-Phosphoglycerate Dehydrogenase Deficiency |
| ***PKHD1*** | Polycystic Kidney Disease, Autosomal Recessive |
| ***PMM2*** | Congenital Disorder of Glycosylation, Type Ia |
| ***POMGNT1*** | Muscle-Eye-Brain Disease and Other POMGNT1-Related Congenital Muscular Dystrophy-Dystroglycanopathies |
| ***PPT1*** | Neuronal Ceroid-Lipofuscinosis (PPT1-Related) |
| ***PROP1*** | Combined Pituitary Hormone Deficiency 2 |
| ***PRPS1*** | Charcot-Marie-Tooth Disease, Type 5 / Arts syndrome |
| ***PSAP*** | Combined SAP Deficiency |
| ***PTS*** | 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency |
| ***PUS1*** | Mitochondrial Myopathy and Sideroblastic Anemia 1 |
| ***PYGM*** | Glycogen Storage Disease, Type V |
| ***RAB23*** | Carpenter Syndrome |
| ***RAG2*** | Omenn Syndrome (RAG2-Related) |
| ***RAPSN*** | Congenital Myasthenic Syndrome (RAPSN-Related) |
| ***RARS2*** | Pontocerebellar Hypoplasia, Type 6 |
| ***RDH12*** | Leber Congenital Amaurosis 13 |
| ***RMRP*** | Cartilage-Hair Hypoplasia |
| ***RPE65*** | Leber Congenital Amaurosis 2 / Retinitis pigmentosa 20 |
| ***RPGRIP1L*** | Joubert Syndrome 7 / Meckel Syndrome 5 / COACH Syndrome |
| ***RS1*** | X-Linked Juvenile Retinoschisis |
| ***RTEL1*** | Dyskeratosis Congenita (RTEL1-Related) |
| ***SACS*** | Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay |
| ***SAMHD1*** | Aicardi-Goutières Syndrome (SAMHD1-Related) |
| ***SEPSECS*** | Progressive Cerebello-Cerebral Atrophy |

| Gene | Disease |
|---|---|
| ***SGCA*** | Limb-Girdle Muscular Dystrophy, Type 2D |
| ***SGCB*** | Limb-Girdle Muscular Dystrophy, Type 2E |
| ***SGCG*** | Limb-Girdle Muscular Dystrophy, Type 2C |
| ***SGSH*** | Mucopolysaccharidosis Type IIIA |
| ***SLC12A3*** | Gitelman Syndrome |
| ***SLC12A6*** | Andermann Syndrome |
| ***SLC17A5*** | Salla Disease |
| ***SLC22A5*** | Primary Carnitine Deficiency |
| ***SLC25A13*** | Citrin Deficiency |
| ***SLC25A15*** | Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome |
| ***SLC26A2*** | Sulfate Transporter-Related Osteochondrodysplasia |
| ***SLC26A4*** | Pendred Syndrome |
| ***SLC35A3*** | Arthrogryposis, Mental Retardation, and Seizures |
| ***SLC37A4*** | Glycogen Storage Disease, Type Ib |
| ***SLC39A4*** | Acrodermatitis Enteropathica |
| ***SLC4A11*** | Corneal Dystrophy and Perceptive Deafness |
| ***SLC6A8*** | Cerebral Creatine Deficiency Syndrome 1 |
| ***SLC7A7*** | Lysinuric Protein Intolerance |
| ***SMARCAL1*** | Schimke Immunoosseous Dysplasia |
| ***SMN1*** | Spinal Muscular Atrophy |
| ***SMPD1*** | Niemann-Pick Disease (SMPD1-Related) |
| ***STAR*** | Lipoid Adrenal Hyperplasia |
| ***SUMF1*** | Multiple Sulfatase Deficiency |
| ***TCIRG1*** | Osteopetrosis 1 |
| ***TECPR2*** | Hereditary Spastic Paraparesis 49 |
| ***TFR2*** | Hemochromatosis, Type 3 |
| ***TGM1*** | Lamellar Ichthyosis, Type 1 |
| ***TH*** | Segawa Syndrome |
| ***TMEM216*** | Joubert Syndrome 2 |
| ***TPP1*** | Neuronal Ceroid-Lipofuscinosis (TPP1-Related) |
| ***TRMU*** | Acute Infantile Liver Failure |
| ***TSFM*** | Combined Oxidative Phosphorylation Deficiency 3 |
| ***TTPA*** | Ataxia With Isolated Vitamin E Deficiency |
| ***TYMP*** | Myoneurogastrointestinal Encephalopathy |
| ***USH1C*** | Usher Syndrome, Type IC |
| ***USH2A*** | Usher Syndrome, Type IIA |
| ***VPS13A*** | Choreoacanthocytosis |
| ***VPS13B*** | Cohen Syndrome |
| ***VPS45*** | Congenital Neutropenia (VPS45-Related) |
| ***VRK1*** | Pontocerebellar Hypoplasia, Type 1A |
| ***VSX2*** | Microphthalmia / Anophthalmia |
| ***WNT10A*** | Odonto-Onycho-Dermal Dysplasia / Schopf-Schulz-Passarge Syndrome |

***† Please note that GJB2 testing includes testing for the two upstream deletions, del(GJB6-D13S1830) and del(GJB6-D13S1854) (PMID: 11807148 and 15994881)***

Integrated GENETICS
LabCorp Specialty Testing Group

# Cystic Fibrosis Mutation Analysis

**Patient Name:** PC, 506-B
**Referring Physician:** David Prescott, MD
**Specimen #:** [redacted]
**Patient ID:** [redacted]
**Client #:** [redacted]
**Case #:** [redacted]

DOB: [redacted]
Sex: M
SSN: [redacted]

Date Collected: [redacted]
Date Received:
LAB ID:
Hospital ID:
Specimen Type: **BLDPER**

[redacted]
Pittsburgh Cryobank
4415 Fifth Avenue
Suite 161
Pittsburgh, PA 15213
USA

**Ethnicity:** African American

**Indication:** Carrier Test / Gamete donor

**RESULTS: Negative for the 97 mutations analyzed**

**INTERPRETATION:**

This individual is negative for the mutations analyzed. This result reduces but does not eliminate the risk to be a CF carrier. See Comments for ethnic-specific risk reductions based on a negative family history.

**COMMENTS:**

**Mutations Detection Rates among Ethnic Groups** — Detection Rates are based on mutation frequencies in patients affected with cystic fibrosis. Among individuals with an atypical or mild presentation (e.g. congential absence of the vas deferens, pancreatitis) detection rates may vary from those provided here.

| Ethnicity | Carrier risk reduction when no family history | Detection rate | References |
|---|---|---|---|
| African American | 1/61 to 1/316 | 81% | ACOG Committee Opinion 486 PMID: 21422883; Heim PMID: 11388756 |
| Ashkenazi Jewish | 1/24 to 1/767 | 97% | ACOG Committee Opinion 486 PMID: 21422883 |
| Asian American | 1/94 to <1/183 | 49-55% | ACOG Committee Opinion 486 PMID: 21422883; Watson PMID: 1384328 |
| Caucasian | 1/25 to 1/343 | 93% | ACOG Committee Opinion 486 PMID: 21422883; Heim PMID: 11388756; Palomaki PMID: 11882786 |
| Hispanic | 1/58 to 1/260 | 78% | ACOG Committee Opinion 486 PMID: 21422883; Heim PMID: 11388756; California Database: (http://www.cdph.ca.gov/programs/GDSP/Documents/CFTabelCurrent.pdf) |
| Jewish, non-Ashkenazi | | Varies by country of origin | Orgad PMID: 11336401; Kerem PMID:10464623 |
| Mixed or Other | | Not Provided | For counseling, consider using the ethnic background with the most conservative risk estimates. |

This interpretation is based on the clinical and family relationship information provided and the current understanding of the molecular genetics of this condition.

**METHOD / LIMITATIONS:**

*CFTR* gene regions are amplified enzymatically. The 97 CF mutations are tested by multiplex allele-specific primer extension, bead array hybridization, and fluorescence detection. The test discriminates between p.F508del and three polymorphisms (p.I506V, p.I507V and p.F508C). Numbering and nomenclature follow Human Genome Variation Society recommendations. Mutations and their legacy names are listed at www.integratedgenetics.com/CFplus. The DNA reference sequence is NG_016465.1. False positive or negative results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationships, or maternal contamination of a fetal sample.



Electronically Signed By: Hui Zhu, Ph.D., FACMG, on [redacted]

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Name: SAMPLE PC 506-B
Date of birth: [redacted]
Gender: M
Hospital/MR #:
Accession #:
Sample Type: BLOOD
Test Code: 8600
Indication: Gamete Donor

Lab Number: 254679
Family #:
Date Collected: [redacted]
Date Received:
Date Reported:

Pittsburgh Cryobank
Tel. No.: 412-687-0335
Fax No: 412-687-0358

## Chromosome Analysis - Blood

**METHOD OF ANALYSIS:** [redacted]
GTG-Banding

| | | | |
|---|---|---|---|
| ***Cultures:*** | 2 | ***No. of images:*** | 7 |
| ***Cells counted:*** | 30 | ***Cells karyotyped:*** | 3 |
| ***Cells analyzed:*** | 5 | ***Band resolution:*** | 525-550 |

**RESULTS:**
46,XY

**INTERPRETATION :**
Normal male chromosome analysis. Analysis of 30 cells rules out 10% mosaicism at the 95% confidence level.

DISCLAIMER:
The resolution of analysis for this standard cytogenetic methodology does not routinely detect subtle rearrangements (<5Mb) or low-level mosaicism. Standard cytogenetic analysis cannot detect microdeletions/microduplications that might be diagnosed with Chromosomal Microarray Analysis. These results do not rule out the possibility of genetic conditions not detectable by cytogenetic analysis. Depending upon the clinical indication, additional testing may be warranted.

**Carlos A. Bacino, M.D., FACMG**
*ABMG Certified Cytogeneticist and Molecular Geneticist*
*Medical Director*

**Weimin Bi, Ph.D.**
*ABMG Certified Clinical Cytogeneticist*
*Assistant Laboratory Director*

Integrated GENETICS
LabCorp Specialty Testing Group

# SMN1 Copy Number Analysis

**Patient Name:** 506-B PC
DOB: [redacted] Age: [redacted]
SSN #: [redacted] Gender: Male

**Specimen #:** [redacted]
Case #: [redacted] Patient ID #: [redacted]
Date Collected: [redacted] Date Received: [redacted]

[redacted]
Pittsburgh Cryobank
4415 Fifth Avenue
Suite 161
Pittsburgh, PA 15213
USA

**Referring Physician:** David Prescott
**Genetic Counselor:**

**Specimen Type:** Peripheral Blood

**Clinical Data:** Carrier Test/Gamete donor

Client Lab ID #:
Hospital ID #:
Specimen ID #:
Specimen(s) Received: 1 - Lavender 7 ml round bottom tube(s)
**Ethnicity:** African American

**RESULTS: SMN1 copy number: 2 (Reduced Carrier Risk)**

**INTERPRETATION:**

**This individual has an SMN1 copy number of two. This result reduces but does not eliminate the risk to be a carrier of SMA. Ethnic specific risk reductions based on a negative family history and an SMN1 copy number of two are provided in the Comments section of this report.**

**COMMENT:**

Spinal muscular atrophy (SMA) is an autosomal recessive disease of variable age of onset and severity caused by mutations (most often deletions or gene conversions) in the survival motor neuron (SMN1) gene. Molecular testing assesses the number of copies of the SMN1 gene. Individuals with one copy of the SMN1 gene are predicted to be carriers of SMA. Individuals with two or more copies have a reduced risk to be carriers. (Affected individuals have 0 copies of the SMN1 gene.)

This copy number analysis cannot detect individuals who are carriers of SMA as a result of either 2 (or very rarely 3) copies of the SMN1 gene on one chromosome and the absence of the SMN1 gene on the other chromosome or small intragenic mutations within the SMN1 gene. This analysis also will not detect germline mosaicism or mutations in genes other than SMN1. Additionally, de novo mutations have been reported in approximately 2% of SMA patients.

| Carrier Frequency and Risk Reductions for Individuals with No Family History of SMA | | | | |
|---|---|---|---|---|
| **Ethnicity** | **Detection Rate[1]** | **Prior Carrier Risk[1]** | **Reduced Carrier Risk for 2 copy result** | **Reduced Carrier Risk for 3 copy result** |
| Caucasian | 94.8% | 1:47 | 1:834 | 1:5,600 |
| Ashkenazi Jewish | 90.5% | 1:67 | 1:611 | 1:5,400 |
| Asian | 93.3% | 1:59 | 1:806 | 1:5,600 |
| Hispanic | 90.0% | 1:68 | 1:579 | 1:5,400 |
| African American | 70.5% | 1:72 | 1:130 | 1:4,200 |
| Asian Indian | 90.2% | 1:52 | 1:443 | 1:5,400 |
| Mixed or Other Ethnic Background | For counseling purposes, consider using the ethnic background with the most conservative risk estimates. | | | |

METHOD/LIMITATIONS: Specimen DNA is isolated and amplified by real-time polymerase chain reaction (PCR) for exon 7 of the SMN1 gene and the internal standard reference genes. A mathematical algorithm is used to calculate and report SMN1 copy numbers of 0, 1, 2 and 3. Based upon this analysis, an upper limit of 3 represents the highest degree of accuracy in reporting SMN1 copy number with statistical confidence. Sequencing of the primer and probe binding sites is performed on all fetal samples and samples with one copy of SMN1 by real-time PCR to rule out the presence of sequence variants which could interfere with analysis and interpretation. False positive or negative results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, erroneous representation of family relationships or contamination of a fetal sample with maternal cells.

REFERENCES:
1. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet 2012; 20:27-32. 2. Prior TW, et al. Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2011; 13(7): 686-694.



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Reported by: /