

4845 Knightsbridge Blvd Suite 200 Columbus, OH 43214 Phone: (614) 451-4375 Fax: (614) 451-5284

# **Genetic Testing Summary**

Enclosed are the genetic testing results for

# **CB** 496

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.



## CARRIER SCREENING REPORT

Patient	Sample	Referring Doctor
Patient Name: Cb 496	Specimen Type: Blood	David Prescott, M.D.
Date of Birth:	Lab #:	Cryobiology, Inc.
Reference #:	Date Collected:	4830-D Knightsbridge Blvd.
Indication: Carrier Testing	Date Received:	Columbus, OH 43214
Test Type: Expanded Carrier Screen (283)	Final Report:	Fax: 614-451-5284

# **RESULT SUMMARY**

# THIS PATIENT WAS TESTED FOR 283 DISEASES. Please see Table 1 for list of diseases tested.

# NEGATIVE for all diseases tested

# Recommendations

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

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.

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

# Interpretation

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 <a href="http://go.sema4.com/residualrisk">http://go.sema4.com/residualrisk</a> 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.



Patient: Cb 496 DOB:

Lab #:

# TEST SPECIFIC RESULTS

# Alpha-thalassemia

**NEGATIVE** for alpha-thalassemia

HBA1 copy number: 2 HBA2 copy number: 2 No pathogenic copy number variants detected HBA1 and HBA2 sequence analysis: No pathogenic or likely pathogenic variants identified Reduced risk of being an alpha-thalassemia carrier (aa/aa)

Genes analyzed: HBA1 (NM 000558.4) and HBA2 (NM 000517.4) Inheritance: Autosomal Recessive

# Recommendations

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

# Interpretation

No pathogenic or likely pathogenic copy number variants or sequence variants were detected in this patient, suggesting that four copies of the alpha-globin gene are present (aa/aa). Typically, individuals have four functional alpha-globin genes: 2 copies of HBA1 and 2 copies of HBA2, whose expression is regulated by a cisacting 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. Individuals with only one functional alpha-globin gene have HbH disease with microcytic, hypochromic hemolytic anemia and hepatosplenomegaly. Loss of all four alpha-globin genes results in Hb Barts syndrome with the accumulation of Hb Barts in red blood cells and hydrops fetalis, which is fatal in utero or shortly after birth.

This individual was negative for all HBA deletions, duplications and variants that were tested. 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 Risks Based on Ethnicity

Ethnicity	Carrier Frequency	Detection Rate	Residual Risk
Caucasian	1 in 500	95%	1 in 10,000
African American	1 in 30	95%	1 in 580
Asian	1 in 20	95%	1 in 380
Worldwide	1 in 25	95%	1 in 480



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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) 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.

# Spinal Muscular Atrophy

**NEGATIVE for spinal muscular atrophy** *SMN1* Copy Number: 2 *SMN2* Copy Number: 1 c.\*3+80T>G: Negative

# Negative copy number result Decreased 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

Consideration of residual risk by ethnicity after a negative carrier screen is recommended, especially in the case of a positive family history for spinal muscular atrophy.

# 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 significantly reduces the risk of being an SMA carrier. 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 negative for this change and is therefore, at a decreased 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	Carrie Frequ	e.r lency	Detection rate	Rea aft rea	ter sul	lual risk r negative .t*	Detec with c.*3+	<b>tion rate</b> <b><i>S11N1</i></b> 80T>G	Re c. ne	sid *3+ gat	u <b>al risk 80T&gt;G</b> ive	Re C. pc	*3- sit	dual risk +80T>G tive
African American	1 ir	85	71%	1 :	in	160	91%		1	in	455	1	in	49
Ashkenazi Jewish	1 ir	1 76	90%	1 :	in	672	93%		1	in	978	1	in	10
East Asian	1 ir	1 53	94%	1 :	in	864	95%		1	in	901	1	in	12
Caucasian	1 ir	48	95%	1 :	in	803	95%		1	in	894	1	in	23
Latino	1 ir	1 63	91%	1 :	in	609	94%		1	in	930	1	in	47
South Asian	1 ir	1 103	87%	1 :	in	637	87%		1	in	637	1	in	608
Sephardic Jewish	1 ir	1 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 EST/MA TE* A Parental follow-up will be requested for confirmation



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Tay-Sachs Disease Enzyme Analysis

# Results: Non-carrier

Specimen	Hexosaminidase Activity	Hex A%	Non-Carrier Range	Comment
Tay-Sachs WBC	1373 nmol/hr/mg	67.6	55.0 - 72.0	Non-Carrier
Tay-Sachs Plasma	447 nmol/hr/ml	59.6	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 Xingwu Lu, Ph.D., FACMG, Assistant Laboratory Director

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





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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<sup>®</sup> *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<sup>®</sup> 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<sup>®</sup> 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 OMO exons were analyzed. Potentially pathogenic single exon deletions and duplications are confirmed by a second method. Analysis of OMO 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 *CYP21A 1P*. 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 *CYP21A 1P*. 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 db 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 nova*. 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 (*GJ82/GJ86*) will only be performed if indicated for confirmation of detected CNVs. **I** *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 numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy numbers of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number of all 27 *CFTR* exons were analyzed. If *GJB2/GJB6* analysis was performed, the copy number 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(GJ86-D13S1830) and del(GJ86-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<sup>TM</sup>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<sup>®</sup> 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  $\Delta\Delta$ Ct 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



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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.

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#### **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.

#### SELECTED REFERENCES

#### **Carrier Screening**

Grody W et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med.* 2013 15:482-3. Fragile X syndrome:

Chen L et al. An information-rich CGG repeat primed PCR that detects the full range of Fragile X expanded alleles and minimizes the need for Southern blot analysis. *J Mol Diag* 2010 12:589-600.

#### Spinal Muscular Atrophy:

Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. *Genet Med.* 2014 16:149-56.

#### Ashkenazi Jewish Disorders:

Scott SA et al. Experience with carrier screening and prenatal diagnosis for sixteen Ashkenazi Jewish Genetic Diseases. *Hum. Mutat.* 2010 31:1-11.

#### Duchenne Muscular Dystrophy:

Flanigan KM et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. *Hum Mutat.* 2009 30:1657-66.

#### Variant Classification:

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.





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## 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	Gene	Disease
ACADM	Medium Chain Acyl-CoA Dehydrogenase Deficiency	CFTR	Cystic Fibrosis
ABCB11	Progressive Familial Intrahepatic Cholestasis, Type 2	СНМ	Choroideremia
ABCC8	Familial Hyperinsulinism (ABCC8-Related)	CHRNE	Congenital Myasthenic Syndrome (CHRNE-Related)
ABCD1	Adrenoleukodystrophy, X-Linked	CIITA	Bare Lymphocyte Syndrome, Type II
ACAD9	Mitochondrial Complex I Deficiency (ACAD9-Related)	CLN3	Neuronal Ceroid-Lipofuscinosis (CLN3-Related)
ACADVL	Very Long Chain Acyl-CoA Dehydrogenase Deficiency	CLN5	Neuronal Ceroid-Lipofuscinosis (CLN5-Related)
ACAT1	Beta-Ketothiolase Deficiency	CLN6	Neuronal Ceroid-Lipofuscinosis (CLN6-Related)
ACOX1	Acyl-CoA Oxidase I Deficiency	CLN8	Neuronal Ceroid-Lipofuscinosis (CLN8-Related)
ACSF3	Combined Malonic and Methylmalonic Aciduria	CLRN1	Usher Syndrome, Type III
ADA	Adenosine Deaminase Deficiency	CNGB3	Achromatopsia
ADAMTS2	Ehlers-Danlos Syndrome, Type VIIC	COL27A1	Steel Syndrome
AGA	Aspartylglycosaminuria	COL4A3	Alport Syndrome (COL4A3-Related)
AGL	Glycogen Storage Disease, Type III	COL4A4	Alport Syndrome (COL4A4-Related)
AGPS	Rhizomelic Chondrodysplasia Punctata, Type 3	COL4A5	Alport Syndrome (COL4A5-Related)
AGXT	Primary Hyperoxaluria, Type 1	COL7A1	Dystrophic Epidermolysis Bullosa
AIRE	Polyglandular Autoimmune Syndrome, Type 1	CPS1	Carbamoylphosphate Synthetase I Deficiency
ALDH3A2	Sjogren-Larsson Syndrome	CPT1A	Carnitine Palmitoyltransferase IA Deficiency
ALDOB	Hereditary Fructose Intolerance	CPT2	Carnitine Palmitoyltransferase II Deficiency
ALG6	Congenital Disorder of Glycosylation, Type Ic	CRB1	Leber Congenital Amaurosis 8 / Retinitis Pigmentosa 12 / Pigmented Paravenous Chorioretinal Atrophy
ALMS1	Alstrom Syndrome	CTNS	Cystinosis
ALPL	Hypophosphatasia	CTSK	Pycnodysostosis
AMT	Glycine Encephalopathy (AMT-Related)	CYBA	Chronic Granulomatous Disease (CYBA-related)
AQP2	Nephrogenic Diabetes Insipidus, Type II	CYBB	Chronic Granulomatous Disease (CYBB-related)
ARSA	Metachromatic Leukodystrophy	CYP11B2	Corticosterone Methyloxidase Deficiency
ARSB	Mucopolysaccharidosis type VI	CYP17A1	Congenital Adrenal Hyperplasia due to 17-Alpha-Hydroxylase Deficiency
ASL	Argininosuccinic Aciduria	CYP21A2	Classic Congenital Adrenal Hyperplasia due to 21- Hydroxylase Deficiency
ASNS	Asparagine Synthetase Deficiency	CYP19A1	Aromatase Deficiency
ASPA	Canavan Disease	CYP27A1	Cerebrotendinous Xanthomatosis
ASS1	Citrullinemia, Type 1	DCLRE1C	Omenn Syndrome / Severe Combined Immunodeficiency, Athabaskan-Type
ATM	Ataxia-Telangiectasia	DHCR7	Smith-Lemli-Opitz Syndrome
ATP6V1B1	Renal Tubular Acidosis and Deafness	DHDDS	Retinitis Pigmentosa 59
ATP7A	Menkes Disease	DLD	Lipoamide Dehydrogenase Deficiency
ATP7B	Wilson Disease	DMD	Duchenne Muscular Dystrophy / Becker Muscular Dystrophy
ATRX	Alpha-Thalassemia Mental Retardation Syndrome	DNAH5	Primary Ciliary Dyskinesia (DNAH5-Related)
BBS1	Bardet-Biedl Syndrome (BBS1-Related)	DNAI1	Primary Ciliary Dyskinesia (DNAI1-Related)
BBS10	Bardet-Biedl Syndrome (BBS10-Related)	DNAI2	Primary Ciliary Dyskinesia (DNAI2-related)
BBS12	Bardet-Biedl Syndrome (BBS12-Related)	DYSF	Limb-Girdle Muscular Dystrophy, Type 2B
BBS2	Bardet-Biedl Syndrome (BBS2-Related)	EDA	Hypohidrotic Ectodermal Dysplasia 1
BCKDHA	Maple Syrup Urine Disease, Type 1a	EIF2B5	Leukoencephalopathy with Vanishing White Matter
BCKDHB	Maple Syrup Urine Disease, Type 1b	EMD	Emery-Dreifuss Myopathy 1
BCS1L	GRACILE Syndrome and Other BCS1L-Related Disorders	ESCO2	Roberts Syndrome
BLM	Bloom Syndrome	ETFA	Glutaric Acidemia, Type Ila
BSND	Bartter Syndrome, Type 4A	ETFDH	Glutaric Acidemia, Type IIc
BTD	Biotinidase Deficiency	ETHE1	Ethylmalonic Encephalopathy
CAPN3	Limb-Girdle Muscular Dystrophy, Type 2A	EVC	Ellis-van Creveld Syndrome (EVC-Related)
CBS	Homocystinuria (CBS-Related)	EYS	Retinitis Pigmentosa 25
CDH23	Usher Syndrome, Type ID	F11	Factor XI Deficiency
CEP290	Leber Congenital Amaurosis 10 and Other CEP290-Related Ciliopathies	F9	Factor IX Deficiency
CERKL	Re initis Pigmentosa 26	FAH	Tyrosinemia, Type I





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Patient: Cb 496

# DOB:

Lab #:

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 21					
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 Encephalopa hy (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	Junc ional Epidermolysis Bullosa (LAMA3-Related)
LAMB3	Junc ional Epidermolysis Bullosa (LAMB3-Related)
LAMC2	Junc ional 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
ММАА	Methylmalonic Acidemia (MMAA-Related)
MMAB	Methylmalonic Acidemia (MMAB-Related)
ММАСНС	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, cbIE 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





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Patient: Cb 496

DOB:

Lab #:

Gene	Disease
NPHS2	Nephrotic Syndrome (NPHS2-Related) / Steroid-Resistant Nephrotic Syndrome
NR2E3	Enhanced S-Cone Syndrome
NTRK1	Congenital Insensitivity to Pain with Anhidrosis
OAT	Omithine Aminotransferase Deficiency
OPA3	3-Methylglutaconic Aciduria, Type III
OTC	Omithine 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	Car ilage-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

- 25					
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	Comeal 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				
тн	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 Wi h 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).



Patient Name: CB496, . Referring Physician: David Prescott, MD Specimen #: Patient ID:





Date Collected: Date Received: LAB ID: Hospital ID: Specimen Type: **BLDPER** 

Ethnicity: Caucasian

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, pancreatilis) 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.

Integrated Genetics is a business unit of Esoterix Genetic Laboratories, LLC, a wholly-owned subsidiary of Laboratory Corporation of America Holdings.

# Cystic Fibrosis Mutation Analysis

Cryobiology, Inc. 4830-D Knightsbridge Boulevard Columbus, OH 43214

Electronically Signed By: Hui Zhu, Ph.D., FACMG,

MUTATIONS ANALYZED					
c.54-5940_273+10250del21kb	c.1973_1985del13insAGAAA	p.R117H	p.R553*		
c.262_263delTT	c.1976delA	p.Y122*	p.A559T		
c.273+1G>A	c.2012delT	p.G178R	p.R560T		
c.273+3A>C	c.2051_2052delAAinsG	p.L206W	p.P574H		
c.274-1G>A	c.2052delA	p.F312del	p.R709*		
c.313delA	c.2052dupA	p.G330*	p.K710*		
c.325_327delTATinsG	c.2175dupA	p.R334W	p.R764*		
c.442delA	c.2657+5G>A	p.T338I	p.Q890*		
c.489+1G>T	c.2737_2738insG	p.R347H	p.R1066C		
c.531delT	c.2988G>A	p.R347P	p.W1089*		
c.579+1G>T	c.2988+1G>A	p.R352Q	p.Y1092*		
c.579+5G>A	c.3039delC	p.[Q359K;T360K]	p.M1101K		
c.580-1G>T	c.3067_3072delATAGTG	p.S364P	p.D1152H		
c.803delA	c.3528delC	p.A455E	p.R1158*		
c.805_806delAT	c.3536_3539delCCAA	p.G480C	p.R1162*		
c.948delT	c.3659delC	p.Q493*	p.S1196*		
c.1155_1156dupTA	c.3717+12191C>T	p.I507del	p.W1204*		
c.1545_1546delTA	c.3744delA	p.F508del	p.Q1238*		
c.1585-1G>A	c.3773dupT	p.V520F	p.S1251N		
c.1680-1G>A	c.3889dupT	p.C524*	p.S1255*		
c.1766+1G>A	p.E60*	p.G542*	p.W1282*		
c.1766+5G>T	p.R75*	p.S549N	p.N1303K		
c.1820_1903del84	p.G85E	p.S549R			
c.1911delG	p.E92*	p.G551D			
c.1923_1931del9insA	p.R117C	p.Q552^			

This test was developed and its performance characteristics determined by Esoterix Genetic Laboratories, LLC. It has not been cleared or approved by the Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

# SMN1 Copy Number Analysis



Referring Physician: David Prescott Genetic Counselor:

Specimen Type: Peripheral Blood

Clinical Data: Carrier Test/Gamete donor

# AMENDED REPORT

Cryobiology, Inc. 4830-D Knightsbridge Boulevard Columbus, OH 43214

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

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:

AMENDED REPORT: [01/02/2018] Patient gender has been corrected. This report supersedes the previous report dated 12/26/2017.

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 <sup>1</sup>	Prior Carrier Risk <sup>1</sup>	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 purpo	ses, consider using th	e ethnic background with the most con	servative 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.

The test was developed and its performance characteristics have been determined by Esoterix Genetic Laboratories, LLC. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. This test must be used in conjunction with clinical assessment, when available. Integrated Genetics is a business unit of Esoterix Genetic Laboratories, LLC, a wholly-owned must be used in conjunction with clinical assessment, when available. Integrated Genetics is a business unit of Esoterix Genetic Laboratories, LLC, a wholly-owned must be used in conjunction with clinical assessment.

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Reported by: JT/jt



DavidPrescott Cryobiology 16144515284 Pg 1/1

www.bmgl.com | genetictest@bmgl.com Ph 1-800-411-4363 | Fx 713-798-2787 2450 Holcombe Blvd, Houston, TX 77021

Name:	DONOR CB 496
Date of birth: Gender:	M
Hospital/MR #:	
Accession #:	
Sample Type:	BLOOD
Test Code:	8600
Indication: Pop	ulation Screening

Lab Number: Family #:
Date Collected:
Date Received:
Date Reported:

David Prescott Cryobiology Tel. No.: 614-451-4375 Fax No: 614-451-5284

# **Chromosome Analysis - Blood**

METHOD OF ANALYSIS: GTG-Banding			
Cultures:	2	No. of images:	30
Cells counted:	30	Cells karyotyped:	3
Cells analyzed:	7	Band resolution:	500-550

# 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.

.<u>\_\_\_</u>\_\_\_

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

Sulinn Berend

Sue Ann Berend, Ph.D., FACMG ABMG Certified Clinical Cytogeneticist

This test was developed and its performance characteristics determined by Baylor Miraca Genetics Laboratories DBA Baylor Genetics (CAP# 2109314 / CLA# 45D0660090; Lab Director: Christine M. Eng, MD). It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Professional component performed by Sue Ann Berend, Ph.D., FACMG, 656 Fall Wood Trail, Fort Worth, TX (CLIA #: 10D2030155).