Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

[redacted]

Genetic Carrier Screen, (CF, FXS, and SMA) with Reflex to Methylation (Temporary Delay as of 01/21/2021 - no referral available)

ARUP test code 3000258

FRAG X Specimen	Whole Blood
Fragile X Allele 1	30 CGG repeats
Fragile X Allele 2	29 CGG repeats
Fragile X Methylation Pattern	Normal
Fragile X Interpretation	See Note

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Negative: This individual has two normal alleles; therefore, she is not a Fragile X carrier. This test does not detect rare mutations in less than 1% of Fragile X cases.

Methylation pattern is normal for gender.

This result has been reviewed and approved by [redacted]

H=High, L=Low, *=Abnormal, C=Critical

	Background Information for Fragile X (FMR1) Characteristics: Fragile X syndrome, the most common heritable form of mental retardation, is characterized by moderate mental retardation in males and mild mental retardation in females, hyperactivity, perseverative speech, social anxiety, poor eye contact, hand flapping or biting, autism spectrum disorders behavioral phenotype, and connective tissue anomalies. Adult males may have physical findings including: macroorchidism, a long narrow face, prominent ears and jaw, and a single palmar crease. Incidence: 1 in 4,000 Caucasian males and 1 in 8,000 Caucasian females; unknown in other ethnicities. Inheritance: X-linked dominant. Penetrance: Reduced in females. Cause: Expansion of the FMR1 gene CGG triplet repeat. Full mutation: >200-230 CGG repeats (methylated) Premutation: 55-200 CGG repeats (unmethylated) Intermediate: 45-54 CGG repeats (unmethylated) Normal: 5-44 CGG repeats (unmethylated) Clinical Sensitivity: 99 percent. Methodology: Triplet repeat-primed polymerase chain reaction (PCR) followed by size analysis using capillary electrophoresis. Methylation-specific PCR analysis is performed for CGG repeat lengths of 55 or greater. Methylation analysis is used to distinguish between premutation and full mutation alleles. Analytic Sensitivity and Specificity: 99 percent. Limitations: Diagnostic errors can occur due to rare sequence variations. See Compliance Statement C: www.aruplab.com/CS
Cystic Fibrosis, Allele 1	Negative
Cystic Fibrosis, Allele 2	Negative
Cystic Fibrosis 5T Variant	Not Applicable
Cystic Fibrosis, 165 Variants, Interp	0 variants

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None of the 165 pathogenic cystic fibrosis (CF) variants tested were detected. The following table can be used to determine the reduction in carrier risk. This table does not apply to individuals with a positive family history who require Bayesian analysis for accurate risk assessment.

Ethnicity	Variant Detection Rate	Carrier Risk Before Test	Carrier Risk After Negative Test
African American	78%	1 in 61	1 in 275
Ashkenazi Jewish	96%	1 in 24	1 in 575
Asian American	55%	1 in 94	1 in 210
Caucasian	92%	1 in 25	1 in 300
Hispanic American	80%	1 in 58	1 in 285

Specimen: Whole Blood
Symptoms: No
Ethnicity: Caucasian
Family Hx: No

This result has been reviewed and approved by Pinar Bayrak-Toydemir, M.D., Ph.D.

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BACKGROUND INFORMATION: Cystic Fibrosis (CFTR), 165 Pathogenic Variants
CHARACTERISTICS OF CLASSIC CYSTIC FIBROSIS (CF): Chronic sino-pulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and obstructive azoospermia. Symptoms of a CFTR-related disorder are often limited to a single organ system such as isolated pancreatitis, bilateral absence of the vas deferens, nasal polyposis, or bronchiectasis.
INCIDENCE: 1 in 2,300 Ashkenazi Jewish, 1 in 2,500 Caucasians, 1 in 13,500 Hispanics, 1 in 15,100 African Americans, 1 in 35,100 Asians.
INHERITANCE: Autosomal recessive.
PENETRANCE: High for severe pathogenic variants, variable for moderate or mild pathogenic variants.
Cause of Classic CF: Two severe, or one severe and one moderate, pathogenic CFTR variants on opposite chromosomes.
Cause of CFTR-Related Disorder: Two pathogenic CFTR variants on opposite chromosomes; two mild, one mild and one severe or one mild and one moderate.
PATHOGENIC VARIANTS TESTED: Variants are listed by standard nomenclature. Legacy names are also provided for the 23 recommended ACMG variants: c.1A>G, p.Met1Val; c.54-5940_273+10250del, Exons 2-3del; c.115C>T, p.Gln39X; c.178G>T, p.Glu60X; c.200C>T, p.Pro67Leu; c.223C>T, p.Arg75X; c.254G>A (Legacy G85E), p.Gly85Glu; c.262_263delTT, p.Leu88IlefsX22 (aka p.Leu88fs); c.273+1G>A, Intronic; c.273+3A>C, Intronic; c.274-1G>A, Intronic; c.274G>A, p.Glu92Lys; c.274G>T, p.Glu92X; c.292C>T, p.Gln98X; c.313delA, p.Ile105SerfsX2 (aka p.Ile105fs); c.325_327delTATinsG, p.Tyr109GlyfsX4 (aka p.Tyr109fs); c.328G>C, p.Asp110His; c.349C>T, p.Arg117Cys; c.350G>A (Legacy R117H), p.Arg117His; c.366T>A, p.Tyr122X; c.442delA, p.Ile148LeufsX5 (aka p.Ile148fs); c.489+1G>T (Legacy 621+1G>T), Intronic; c.531delT, p.Ile177MetfsX12 (aka p.Ile177fs); c.532G>A, p.Gly178Arg; c.579+1G>T (Legacy 711+1G>T), Intronic; c.579+5G>A, Intronic;

c.579+3A>G, Intronic; c.580-1G>T, Intronic; c.595C>T, p.His199Tyr; c.613C>T, p.Pro205Ser; c.617T>G, p.Leu206Trp; c.658C>T, p.Gln220X; c.680T>G; p.Leu227Arg; c.720_741delAGGGAGAATGATGATGAAGTAC, p.Gly241GlufsX13 (aka p.Gly241fs); c.803delA, p.Asn268IlefsX17 (aka p.Asn268fs); c.805_806delAT, p.Ile269ProfsX4 (aka p.Ile269fs); c.933_935delCTT, p.Phe312del; c.948delT, p.Phe316LeufsX12 (aka p.Phe316fs); c.988G>T, p.Gly330X; c.1000C>T (Legacy R334W), p.Arg334Trp; c.1007T>A, p.Ile336Lys; c.1021T>C, p.Ser341Pro; c.1022_1023insTC, p.Phe342HisfsX28 (aka p.Phe342fs); c.1040G>A, p.Arg347His; c.1040G>C (Legacy R347P), p.Arg347Pro; c.1055G>A, p.Arg352Gln; c.1081delT, p.Trp361GlyfsX8 (aka p.Trp361fs); c.1116+1G>A, Intronic; c.1127_1128insA, p.Gln378AlafsX4 (aka p.Gln378fs); c.1153_1154insAT, p.Asn386IlefsX3 (aka p.Asn386fs); c.1202G>A, p.Trp401X; c.1203G>A, p.Trp401X; c.1209+1G>A, Intronic; c.1329_1330insAGAT, p.Ile444ArgfsX3 (aka p.Ile444fs); c.1340delA; p.Lys447ArgfsX2 (aka p.Lys447fs); c.1364C>A (Legacy A455E), p.Ala455Glu; c.1393-1G>A, Intronic; c.1397C>A, p.Ser466X; c.1397C>G, p.Ser466X; c.1400T>C, p.Leu467Pro; c.1418delG, p.Gly473GlufsX54 (aka p.Gly473fs); c.1438G>T, p.Gly480Cys; c.1466C>A, p.Ser489X; c.1475C>T, p.Ser492Phe; c.1477C>T, p.Gln493X; c.1519_1521delATC (Legacy I507del), p.Ile507del; c.1521_1523delCTT (Legacy F508del), p.Phe508del; c.1545_1546delTA, p.Tyr515X; c.1558G>T, p.Val520Phe; c.1572C>A, p.Cys524X; c.1573C>T, p.Gln525X; c.1585-1G>A (Legacy 1717-1G>A), Intronic; c.1585-8G>A, Intronic; c.1624G>T (Legacy G542X), p.Gly542X; c.1645A>C, p.Ser549Arg; c.1646G>A, p.Ser549Asn; c.1647T>G, p.Ser549Arg; c.1651G>A, p.Gly551Ser; c.1652G>A (Legacy G551D), p.Gly551Asp; c.1654C>T, p.Gln552X; c.1657C>T (Legacy R553X), p.Arg553X; c.1675G>A, p.Ala559Thr; c.1679G>A, p.Arg560Lys; c.1679G>C (Legacy R560T), p.Arg560Thr; c.1679+1.6kbA>G, Intronic; c.1680-1G>A, Intronic; c.1703delT, p.Leu568CysfsX4 (aka p.Leu568fs); c.1705T>G, p.Tyr569Asp; c.1721C>A, p.Pro574His; c.1753G>T, p.Glu585X; c.1766+1G>A (Legacy 1898+1G>A), Intronic; c.1766+3A>G, Intronic; c.1792_1798delAAAACTA, p.Lys598GlyfsX11 (aka p.Lys598fs); c.1911delG, p.Gln637HisfsX26 (aka p.Gln637fs); c.1923_1931del9insA, p.Ser641ArgfsX5 (aka p.Ser641fs); c.1973_1985del13insAGAAA, p.Arg658LysfsX4 (aka p.Arg658fs); c.1976delA; p.Asn659IlefsX4 (aka p.Asn659fs); c.2012delT, p.Leu671X; c.2051_2052del, p.Lys684ThrfsX4; c.2051_2052delinsG (aka c.2051_2delinsG), p.Lys684SerfsX38; c.2052delA (Legacy 2184delA), p.Lys684AsnfsX38; c.2125C>T, p.Arg709X; c.2128A>T, p.Lys710X; c.2175_2176insA, p.Glu726ArgfsX4 (aka p.Glu726fs); c.2195T>G, p.Leu732X; c.2215delG, p.Val739TyrfsX16 (aka p.Val739fs); c.2290C>T, p.Arg764Ter; c.2453delT, p.Leu818TrpfsX3 (aka p.Leu818fs); c.2464G>T, p.Glu822X; c.2490+1G>A, Intronic; c.2491G>T, p.Glu831X; c.2537G>A, p.Trp846X; c.2538G>A; p.Trp846X; c.2551C>T, p.Arg851X; c.2583delT, p.Phe861LeufsX3 (aka p.Phe861fs); c.2657+5G>A (Legacy 2789+5G>A), Intronic; c.2668C>T, p.Gln890X; c.2737_2738insG, p.Tyr913X; c.2780T>C, p.Leu927Pro; c.2810_2811insT, p.Val938GlyfsX37 (aka p.Val938fs); c.2834C>T, p.Ser945Leu; c.2875delG, p.Ala959HisfsX9 (aka p.Ala959fs); c.2908G>C, p.Gly970Arg; c.2988+1G>A (Legacy 3120+1G>A), Intronic; c.2988G>A, Intronic; c.2989-1G>A, Intronic; c.3039delC, p.Tyr1014ThrfsX9 (aka p.Tyr1014fs); c.3067_3072delATAGTG, p.Ile1023_Val1024del (aka I1023_V1024del); c.3140-26A>G, Intronic; c.3194T>C, p.Leu1065Pro; c.3196C>T, p.Arg1066Cys; c.3197G>A, p.Arg1066His; c.3230T>C, p.Leu1077Pro; c.3266G>A, p.Trp1089X; c.3276C>A, p.Tyr1092X; c.3276C>G, p.Tyr1092X; c.3302T>A, p.Met1101Lys; c.3310G>T, p.Glu1104X; c.3472C>T, p.Arg1158X; c.3484C>T (Legacy R1162X), p.Arg1162X; c.3528delC (Legacy 3659delC), p.Lys1177SerfsX15 (aka p.Lys1177fs); c.3536_3539del, p.Thr1179AsnfsX12 (aka p.Thr1179fs); c.3587C>G, p.Ser1196X; c.3611G>A, p.Trp1204X; c.3612G>A, p.Trp1204X; c.3659delC, p.Thr1220LysfsX8 (aka p.Thr1220fs); c.3691delT, p.Ser1231ProfsX4 (aka p.Ser1231fs); c.3712C>T, p.Gln1238X; c.3718+2477C>T (Legacy 3849+10kbC>T), Intronic; c.3731G>A, p.Gly1244Glu; c.3744delA, p.Lys1250ArgfsX9 (aka p.Lys1250fs); c.3752G>A, p.Ser1251Asn; c.3763T>C, p.Ser1255Pro; c.3764C>A, p.Ser1255X; c.3773_3774insT,

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	p.Leu1258PhefsX7 (aka p.Leu1258fs); c.3846G>A (Legacy W1282X), p.Trp1282X; c.3873+1G>A, Intronic; c.3909C>G (Legacy N1303K), p.Asn1303Lys; c.3937C>T, p.Gln1313X; c.3964-78_4242+577del, Exons 22-23del; c.4028delG, p.Gly1343AlafsX4 (aka p.Gly1343fs); c.4046G>A, p.Gly1349Asp; c.4077_4080delTGTTinsAA, p.Val1360fsX3 (aka p.Val1360fs); c.4111G>T, p.Glu1371X; c.4251delA, p.Glu1418ArgfsX14 (aka p.Glu1418fs). The IVS-8 variant, c.1210-12[5], will be reported only when R117H is detected or in patients who are reported to be symptomatic. CLINICAL SENSITIVITY: Ashkenazi Jewish 96 percent; Caucasian 92 percent; Hispanic 80 percent; African American 78 percent; Asian American 55 percent. METHODOLOGY: Polymerase chain reaction (PCR) and fluorescence monitoring. Analytical Sensitivity & Specificity: 99 percent. LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Only the 165 pathogenic CFTR variants and 5T variant (listed above) will be interrogated. See Compliance Statement C: www.aruplab.com/CS
SMA Copy Number, Specimen	Whole Blood
SMA Copy Number, Symptoms	No
SMA Copy Number, SMN1 Copies	2 copies
SMA Copy Number, SMN2 Copies	2 copies
SMA Copy Number, Linked Variant	Not Present
SMA Copy Number, Int	See Note

H=High, L=Low, *=Abnormal, C=Critical

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Indication for testing: Carrier screening for spinal muscular atrophy (SMA).

Result: Two copies of SMN1 detected.

Interpretation: Two copies of the SMN1 gene were detected by multiplex ligation-dependent probe amplification (MLPA); therefore, this individual's risk to be a carrier of spinal muscular atrophy (SMA) has been reduced but not eliminated. This test is unable to differentiate individuals with one copy of SMN1 on each chromosome (1/1) from individuals with two copies of SMN1 on one chromosome and zero on the other (2/0, known as silent carriers). The linked variants sometimes associated with SMN1 duplication were not detected in this individual; therefore residual risk to be a silent carrier (2/0) can be further reduced but not eliminated. See the table below for ethnicity-specific post-test risk to be a SMA carrier given this result, assuming no family history of SMA. Bayesian statistical analysis is necessary to determine risk for those with a positive family history. Please refer to the background information included in this report for the limitations of this test.

Ethnicity	Carrier Freq	Detection	Post-test Carrier Risk
Ash Jewish	1 in 41	94 percent	1 in 580
Asian	1 in 53	93 percent	1 in 702
Afr American	1 in 66	71 percent	1 in 396
Hispanic	1 in 117	91 percent	1 in 1762
Caucasian	1 in 35	95 percent	1 in 769

References for the table above:
Hendrickson et al. Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet 2009;46:641-644.
Luo et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med. 2014 Feb;16(2):149-56.

2 copies of the SMN2 gene was/were detected by MLPA. In individuals affected with SMA, SMN2 copy number may inversely correlate with disease severity; however, SMN2 copy number cannot predict phenotype with certainty.

Recommendations: Genetic counseling is recommended.

This result has been reviewed and approved by Elaine Lyon, Ph.D.

BACKGROUND INFORMATION: Spinal Muscular Atrophy (SMA) Copy Number Analysis

CHARACTERISTICS: Spinal muscular atrophy (SMA) is the most common lethal genetic disease in children, and is characterized by progressive muscle weakness due to degeneration of the lower motor neurons. Onset ranges from before birth to adulthood and severity is highly variable. Individuals with SMA have no (zero) functioning copies of the SMN1 gene that produces survival motor neuron protein; most (95 percent) have homozygous loss of SMN1 due to deletion or gene conversion, while some (5 percent) have a sequence variant in one remaining copy of SMN1. The SMN2 gene, adjacent and highly homologous to SMN1, produces lower levels of survival motor neuron protein compared to SMN1. Disease severity has been shown to be modified by SMN2 gene copy number in some cases, but phenotype cannot be predicted with certainty. Two variants that are part of a haplotype associated with SMN1 duplication in silent carriers (2 copies of SMN1 on one chromosome with zero copies on the other) are reported as present or not present. The presence of these variants, particularly in Ashkenazi Jews and Asians, increases the likelihood that 2 copies of SMN1 are on the same chromosome but this is not definitive.
INHERITANCE: Autosomal recessive
CAUSE: Pathogenic mutations in the SMN1 gene.
VARIANTS TESTED: For copy number: SMN1(NM_000344.3) exon 7 c.840C and exon 8 c.*239G, and SMN2 (NM_017411.3) exon 7 c.840T. For haplotype associated with SMN1 duplication (silent carriers): SMN1 c.*3+80T>G (rs143838139) and c.*211_*212del (rs200800214).
CLINICAL SENSITIVITY: 95-98 percent in individuals affected with SMA. Detection rate for carrier screening is 95 percent in Caucasians, 94 percent in Ashkenazi Jewish, 93 percent in Asians, 71 percent in African Americans, and 91 percent in Hispanics.
METHODOLOGY: Multiplex probe ligation-dependent amplification (MLPA)
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Single base pair substitutions, small deletions/duplications, regulatory region mutations, and deep intronic mutations will not be detected. This test is unable to determine chromosomal phase of SMN1 or SMN2 copies. Even if the variants associated with SMN1 duplication are detected, the test cannot definitively differentiate individuals with one or more copies of SMN1 on each chromosome from individuals with two or more copies of SMN1 on one chromosome and zero on the other (silent carriers).

Counseling and informed consent are recommended for genetic testing. Consent forms are available online at www.aruplab.com.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
FRAG X Specimen	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
Fragile X Allele 1	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
Fragile X Allele 2	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
Fragile X Methylation Pattern	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
Fragile X Interpretation	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
Cystic Fibrosis, Allele 1	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:20 00 PM
Cystic Fibrosis, Allele 2	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:20 00 PM
Cystic Fibrosis 5T Variant	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:20 00 PM
Cystic Fibrosis, 165 Variants, Interp	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:20 00 PM
SMA Copy Number, Specimen	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
SMA Copy Number, Symptoms	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
SMA Copy Number, SMN1 Copies	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
SMA Copy Number, SMN2 Copies	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
SMA Copy Number, Linked Variant	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM
SMA Copy Number, Int	18-058-118094	2/27/2018 4:12:00 PM	2/27/2018 4:13 09 PM	2/27/2018 4:24:00 PM

END OF CHART