ARUP LABORATORIES
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Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Genetic Carrier Screen, (CF, FXS, and SMA) with Reflex to Methylation

ARUP test code 3000258

FRAG X Specimen	Whole Blood
Fragile X Allele 1	69 CGG repeats
Fragile X Allele 2	Not Applicable CGG repeats
Fragile X Methylation Pattern	Not Applicable
Fragile X Interpretation	See Note

This individual has one FMR1 allele in the premutation range. Although he is not affected with fragile X syndrome, he is at risk for developing fragile X-associated tremor/ataxia syndrome (FXTAS); approximately 40-45% of males with a premutation develop FXTAS after age 50 (Am J Hum Genet. 2004; 74:805-816). None of his sons, but all of his daughters will inherit the premutation. Genetic consultation is recommended.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Fragile X (FMR1) with Reflex to Methylation Analysis
CHARACTERISTICS OF FRAGILE X SYNDROME (FXS): Affected males have moderate intellectual disability, hyperactivity, perseverative speech, social anxiety, poor eye contact, hand flapping or biting, autism spectrum disorders and connective tissue anomalies in males. Females are usually less severely affected than males. FXS is caused by FMR1 full mutations.
CHARACTERISTICS OF FRAGILE X TREMOR ATAXIA SYNDROME (FXTAS): Onset of progressive ataxia and intention tremor typically after the fourth decade of life. Females also have a 21 percent risk for primary ovarian insufficiency. FXTAS is caused by FMR1 premutations.
Incidence of FXS: 1 in 4,000 Caucasian males and 1 in 8,000 Caucasian females.
INHERITANCE: X-linked.
PENETRANCE OF FXS: Complete in males; 50 percent in females.
PENETRANCE OF FXTAS: 47 percent in males and 17 percent in females >50 years of age.
CAUSE: Expansion of the FMR1 gene CGG triplet repeat.
  Full mutation: typically >200 CGG repeats (methylated).
  Premutation: 55 to approx 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 >100 to distinguish between premutation and full mutation alleles.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent; estimated precision of sizing for intermediate and premutation alleles is within 2-3 CGG repeats.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Rare FMR1 variants unrelated to trinucleotide expansion will not be detected. A specific CGG repeat size estimate is not provided for full mutation alleles. AGG trinucleotide interruptions within the FMR1 CGG repeat tract are not assessed.

PHENOTYPE	NUMBER OF CGG REPEATS
Unaffected	<45
Intermediate	45-54
Premutation	55-200
Affected	>200

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Cystic Fibrosis, Allele 1	p.Phe508del	*
Cystic Fibrosis, Allele 2	p.Phe508del	*
Cystic Fibrosis 5T Variant	Negative	
CF Expanded Variant Panel Interp	See Note	

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Two copies of a pathogenic CFTR variant were identified by the cystic fibrosis (CF) variant panel. This result is consistent with a diagnosis of CF. Genetic consultation and referral to a CF clinic for disease management is indicated. Adult family members and current (or future) reproductive partners should be offered CF carrier screening.

Specimen: Whole Blood
Symptoms: Yes
Family History: Unknown

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR), Expanded Variant Panel
CHARACTERISTICS OF CYSTIC FIBROSIS (CF): Chronic sinopulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and obstructive azoospermia. Symptoms of CFTR-related disorders include: pancreatitis, bilateral absence of the vas deferens, nasal polyposis, and 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 and variable for variants of varying clinical consequences.
Cause of CF: Two severe pathogenic CFTR variants on opposite chromosomes.
Cause of CFTR-related disorders: Two pathogenic CFTR variants on opposite chromosomes, at least one of which is classified as mild or a variant of varying clinical consequences.
VARIANTS TESTED:
*Note: 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+10250del21kb, 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.722_743del, p.Gly241GlufsX13 (aka p.Gly241fs); c.803delA, p.Asn268IlefsX17 (aka p.Asn268fs); c.805_806delAT, p.Ile269ProfsX4 (aka p.Ile269fs); c.935_937delTCT, 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.1021_1022dupTC, 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.1130dupA, p.Gln378AlafsX4 (aka p.Gln378fs); c.1155_1156dupTA, p.Asn386IlefsX3 (aka p.Asn386fs); c.1202G>A, p.Trp401X; c.1203G>A, p.Trp401X; c.1209+1G>A, Intronic; c.1327_1330dupGATA, 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.1680-886A>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.2175dupA, 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.2810dupT, 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.3532_3535dupTCAA, p.Thr1179IlefsX17 (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.3773dupT, 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.4025_4028dup, p.Cys1344GlyfsX16 (aka p.C1344fs); 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: Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF)
Analytical sensitivity and specificity: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Only the CFTR variants listed above and 5T variant will be interrogated.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

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SMA Copy Number, Specimen	Whole Blood
SMA Copy Number, Symptoms	No
SMA Copy Number, SMN1 Copies	1 copy *
SMA Copy Number, SMN2 Copies	2 copies
SMA Copy Number, Linked Variant	Not Present
SMA Copy Number, Int	See Note Indication for testing: Carrier screening for spinal muscular atrophy (SMA). Result: SMN1 gene copies: 1 SMN2 gene copies: 2 copies Linked variant: not detected Interpretation: One copy of the SMN1 gene was detected by multiplex ligation-dependent probe amplification (MLPA); therefore, this individual is predicted to be at least a carrier of spinal muscular atrophy (SMA). Please refer to the background information included in this report for the clinical sensitivity and limitations of this test. Recommendations: Genetic counseling is recommended. This individual's reproductive partner and adult family members should be offered SMA carrier screening. This result has been reviewed and approved by [redacted]

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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 functioning copies of the SMN1 gene. Most (95 percent) have homozygous loss of SMN1 due to deletion or gene conversion, while a minority (5 percent) have a deletion of SMN1 on one chromosome and a SMN1 sequence variant on the other. 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, though phenotype cannot be predicted with certainty. An SMN1 variant, c.*3+80T>G (rs143838139), that is part of a haplotype associated with SMN1 duplication in silent carriers (2 copies of SMN1 on one chromosome and no copies on the other), particularly in Ashkenazi Jews, increases the likelihood that 2 copies of SMN1 are on the same chromosome.
INHERITANCE: Autosomal recessive.
CAUSE: Pathogenic variants 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).
CLINICAL SENSITIVITY: 95-98 percent in individuals affected with SMA. Detection rate for carrier screening is 90 percent in African Americans, 93 percent in Ashkenazi Jewish, 93 percent in Asians, 95 percent in Caucasians, and 93 percent in Hispanics.
METHODOLOGY: Multiplex probe ligation-dependent amplification (MLPA) to detect SMN1 and SMN2 copy number and presence or absence of the SMN1 linked variant c.*3+80T>G (rs143838139).
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Single base pair substitutions, small deletions/duplications, and regulatory region and deep intronic variants will not be detected. This test is unable to determine chromosomal phase of SMN1 or SMN2 copies. Even if the linked variant associated with SMN1 duplication is detected, the test cannot definitively differentiate between 1+ copies of SMN1 on each chromosome from 2+ copies of SMN1 on one chromosome and none on the other (silent carriers).

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
FRAG X Specimen	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Fragile X Allele 1	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Fragile X Allele 2	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Fragile X Methylation Pattern	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Fragile X Interpretation	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cystic Fibrosis, Allele 1	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cystic Fibrosis, Allele 2	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cystic Fibrosis 5T Variant	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CF Expanded Variant Panel Interp	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, Specimen	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, Symptoms	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, SMN1 Copies	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, SMN2 Copies	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, Linked Variant	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
SMA Copy Number, Int	23-243-114256	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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