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Patient Report

Patient Age/Sex: 38 years Female

**Specimen Collected: 14-Mar-22 14:03**

**Genetic Carrier Screen 3 Disord w/Rflx** | **Received: 14-Mar-22 14:03** | **Report/Verified: 16-Mar-22 12:53**

| Procedure | Result | Units | Reference Interval |
|---|---|---|---|
| FRAG X Specimen | Whole Blood | | |
| Fragile X Allele 1 | 30 | CGG repeats | |
| Fragile X Allele 2 | 29 | CGG repeats | |
| Fragile X Methylation Pattern | Not Applicable | | |
| Fragile X Interpretation | See Note [f1 i1] | | |
| Cystic Fibrosis,Allele 1 | Negative | | |
| Cystic Fibrosis,Allele 2 | Negative | | |
| Cystic Fibrosis 5T Variant | Not Applicable | | |
| CF Expanded Variant Panel Interp | 0 variants [f2 i2] | | |
| SMA Copy Number, Specimen | Whole Blood | | |
| SMA Copy Number, Symptoms | No | | |
| SMA Copy Number,SMN1 Copies | 2 copies | | |
| SMA Copy Number,SMN2 Copies | 1 copy | | |
| SMA Copy Number,Linked Variant | Not Present | | |
| SMA Copy Number,Int | See Note [f3 i3] | | |

## Result Footnote

f1: Fragile X Interpretation

This individual has two FMR1 alleles with CGG sizes in the normal range; therefore, she is predicted to be neither affected with, nor a carrier of, fragile X syndrome (FXS). This test does not detect rare FMR1 variants causing less than 1% of FXS.

This result has been reviewed and approved by Rong Mao, M.D.

f2: CF Expanded Variant Panel Interp

None of the 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 |
|---|---|---|---|

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

## Result Footnote

f2: CF Expanded Variant Panel Interp

| | | | |
|---|---|---|---|
| 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
Family History: No

This result has been reviewed and approved by Rong Mao, M.D.

f3: SMA Copy Number, Int

Indication for testing: Carrier screening for spinal muscular atrophy (SMA).
Result:
SMN1 gene copies: 2
SMN2 gene copies: 1 copy
Linked variant: not 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) is reduced. See the table below for the ethnicity-specific post-test risk to be a carrier of SMA. Bayesian analysis is necessary to determine carrier risk for those with a positive family history. To review test limitations, see the background information in this report.

| Ethnicity | Carrier Risk Before Test(2) | Detection Rate(1) | Carrier Risk After Test(1) |
|---|---|---|---|
| Afr American | 1 in 72 | 90 percent | 1 in 375 |
| Ash Jewish | 1 in 67 | 93 percent | 1 in 918 |
| Asian | 1 in 59 | 93 percent | 1 in 907 |
| Caucasian | 1 in 47 | 95 percent | 1 in 921 |
| Hispanic | 1 in 68 | 93 percent | 1 in 906 |

References:
(1)Feng, Yanming et al. The next generation of population-based spinal muscular atrophy carrier screening: comprehensive pan-ethnic SMN1 copy-number and sequence variant analysis by massively parallel sequencing. Gen Med 2017; 19; 936-44.
(2)Sugarman, Elaine et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72400 specimens. Eur J Hum Gen 2012; 20; 27-32.

This result has been reviewed and approved by Rong Mao, M.D.

## Test Information

i1: Fragile X Interpretation

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.

## Test Information

i1: Fragile X Interpretation

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 |

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

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

i2: CF Expanded Variant Panel Interp

BACKGROUND INFORMATION: Cystic Fibrosis (CFTR),
Expanded Variant Panel
CHARACTERISTICS OF CYSTIC FIBROSIS (CF): Chronic sino-pulmonary disease, gastrointestinal malabsorption/pancreatic insufficiency, and obstructive

## Test Information

i2: CF Expanded Variant Panel Interp

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;

## Test Information

i2: CF Expanded Variant Panel Interp

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: Polymerase chain reaction (PCR) and fluorescence monitoring.

## Test Information

i2: CF Expanded Variant Panel Interp

Analytical Sensitivity & 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 US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

i3: SMA Copy Number, Int

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

## Test Information

i3: SMA Copy Number, Int

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).

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

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.