SAMPLE REPORT

Integrated GENETICS
LabCorp Specialty Testing Group

Inheritest® Core Panel

Patient Name: LASTNAME, FIRSTNAME
Referring Physician: REF. PHYSICIAN NAME
Specimen #: 00000000-00
Patient #: 00000000
Client #: 000000
Case #:00000000

DOB: MM/DD/YYYY
Sex: Female
Lab ID:
Hospital ID:
Specimen Type: Peripheral Blood

Date Collected: MM/DD/YYYY
Date Received: MM/DD/YYYY

CLIENT ADDRESS

Ethnicity: Ashkenazi Jewish
Indication: Screening

Disorder *(Gene)*	Results	Interpretation
Cystic fibrosis (*CFTR*)	Negative for the mutations analyzed	These results reduce, but do not eliminate, the chance to be a carrier. For risk reductions see Information Table.
Spinal muscular atrophy (*SMN1*)	AT RISK	2 copies of *SMN1*; positive for c.*3+80T>G SNP. At risk to be a silent carrier (2+0). For ethnic-specific risk revisions see Information Table. Genetic counseling is recommended.
Fragile X syndrome (*FMR1*)	PCR: 31 and 33 repeats	Negative: not a carrier of a fragile X expansion mutation. This result is not associated with fragile X syndrome.

Genetic counseling services are available. To access Integrated Genetics Genetic Counselors please visit www.integratedgenetics.com/genetic-counseling or call (855)GC-CALLS (855-422-2557).

ADDITIONAL CLINICAL INFORMATION

Cystic fibrosis: Cystic fibrosis (CF) is an autosomal recessive disorder with variable severity and age of onset. Symptoms of classic CF include elevated sweat chloride levels, progressive lung disease, pancreatic insufficiency, and male infertility. Individuals with mild CF may have pancreatic sufficiency. *CFTR*-related disorders include pancreatitis, bronchiectasis, and isolated male infertility due to congenital absence of the vas deferens. Treatment is primarily dietary and supportive. Genotype-targeted therapies may be available for some individuals. In severely affected individuals, lung transplantation may be indicated. (Moskowitz, PMID:20301428)

Spinal muscular atrophy: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder with variable age at onset and severity, characterized by progressive degeneration of the lower motor neurons in the spinal cord and brain stem, leading to muscle weakness, and in its most common form, respiratory failure by age two. Complications of SMA may include poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint deformities. In severely affected individuals, abnormal fetal ultrasound findings may include congenital joint contractures, polyhydramnios, and decreased fetal movement (Korinthenberg, PMID:9307259). Treatment is supportive. Targeted therapies may be available for some individuals. Approximately 94% of affected individuals have 0 copies of the *SMN1* gene; in these individuals an increase in the number of copies of the *SMN2* gene correlates with reduced disease severity (Feldkotter, PMID:11791208). Individuals with one copy of the *SMN1* gene are predicted to be carriers of SMA; those with two or more copies have a reduced carrier risk. For individuals with two copies of the *SMN1* gene, the presence or absence of the variant c.*3+80T>G correlates with an increased or decreased risk, respectively, of being a silent carrier (2+0) (Luo, PMID 23788250; Feng, PMID 28125085). Genetic counseling is recommended to discuss the potential clinical and/or reproductive implications of these results, as well as recommendations for testing family members and, when applicable, this individual's partner.

Fragile X syndrome: Fragile X syndrome is an X-linked disorder of intellectual disability with variable severity. Expansions of

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CGG repeat sequences in the *FMR1* gene account for 99% of mutations causing fragile X syndrome. Interpretation of repeat expansion results is based on the following ranges: Negative: <45 repeats; intermediate: 45-54 repeats; premutation: 55-200 repeats; full mutation: >200 repeats. The risk for a premutation allele of 55-90 repeats to expand to a full mutation in offspring, when transmitted by a carrier female, is reduced with increasing number of AGG interruptions in the CGG repeat sequence (Yrigollen, PMID:22498846; Nolin, PMID:25210937). Greater than 99% of males and approximately 50% of females with the full mutation are intellectually disabled. Other signs and symptoms may include delayed speech and language skills, autism, hyperactivity, developmental delay, increased susceptibility to seizures, macroorchidism in males, a long, narrow face with prominent ears, and joint laxity. Individuals with a premutation do not have fragile X syndrome, but may have an increased risk for fragile X-related disorders. Females may have fragile X-associated primary ovarian insufficiency (FXPOI), which can cause infertility or early menopause. Most males with a premutation and some females are at risk for fragile X-associated tremor and ataxia syndrome (FXTAS), which can affect balance and is associated with tremor and memory problems in older individuals. Treatment is supportive and focuses on educational and behavioral support and management of symptoms. (Santoro, PMID:22017584).

METHOD / LIMITATIONS:

Cystic fibrosis: *CFTR* gene regions are amplified enzymatically. 97 targeted CF mutations, listed below, 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. The DNA reference sequence is NG_016465.1. Legacy mutation names are available at www.integratedgenetics.com/CFplus.

c.54-5940_273+10250del21kb (p.S18fs), c.178G>T (p.E60*), c.223C>T (p.R75*), c.254G>A (p.G85E), c.262_263delTT (p.L88fs), c.273+1G>A, c.273+3A>C, c.274-1G>A, c.274G>T (p.E92*), c.313delA (p.I105fs), c.325_327delTATinsG (p.Y109fs), c.349C>T (p.R117C), c.350G>A (p.R117H), c.366T>A (p.Y122*), c.442delA (p.I148fs), c.489+1G>T, c.531delT (p.I177fs), c.532G>A (p.G178R), c.579+1G>T, c.579+5G>A, c.580-1G>T, c.617T>G (p.L206W), c.803delA (p.N268fs), c.805_806delAT (p.I269fs), c.935_937delTCT (p.F312del), c.948delT (p.F316fs), c.988G>T (p.G330*), c.1000C>T (p.R334W), c.1013C>T (p.T338I), c.1040G>A (p.R347H), c.1040G>C (p.R347P), c.1055G>A (p.R352Q), c.[1075C>A;1079C>A] (p.[Q359K;T360K]), c.1090T>C (p.S364P), c.1155_1156dupTA, c.1364C>A (p.A455E), c.1438G>T (p.G480C), c.1477C>T (p.Q493*), c.1519_1521delATC (p.I507del), c.1521_1523delCTT (p.F508del), c.1545_1546delTA (p.Y515*), c.1558G>T (p.V520F), c.1572C>A (p.C524*), c.1585-1G>A, c.1624G>T (p.G542*), c.1646G>A (p.S549N), c.1647T>G (p.S549R), c.1652G>A (p.G551D), c.1654C>T (p.Q552*), c.1657C>T (p.R553*), c.1675G>A (p.A559T), c.1679G>C (p.R560T), c.1680-1G>A, c.1721C>A (p.P574H), c.1766+1G>A, c.1766+5G>T, c.1820_1903del84 (p.M607_Q634del), c.1911delG (p.Q637fs), c.1923_1931del9insA (p.S641fs), c.1973_1985del13insAGAAA (p.R658fs), c.1976delA (p.N659fs), c.2012delT, c.2051_2052delAAinsG (p.K684fs), c.2052delA (p.K684fs), c.2052dupA (p.Q685fs), c.2125C>T (p.R709*), c.2128A>T (p.K710*), c.2175dupA (p.E726fs), c.2290C>T (p.R764*), c.2657+5G>A, c.2668C>T (p.Q890*), c.2737_2738insG (p.Y913*), c.2988G>A, c.2988+1G>A, c.3039delC (p.Y1014fs), c.3067_3072delATAGTG (p.I1023_V1024del), c.3196C>T (p.R1066C), c.3266G>A (p.W1089*), c.3276C>A (p.Y1092*), c.3276C>G (p.Y1092*), c.3302T>A (p.M1101K), c.3454G>C (p.D1152H), c.3472C>T (p.R1158*), c.3484C>T (p.R1162*), c.3528delC (p.K1177fs), c.3536_3539delCCAA (p.T1179fs), c.3587C>G (p.S1196*), c.3612G>A (p.W1204*), c.3659delC (p.T1220fs), c.3712C>T (p.Q1238*), c.3717+12191C>T, c.3744delA (p.K1250fs), c.3752G>A (p.S1251N), c.3764C>A (p.S1255*), c.3773dupT (p.L1258fs), c.3846G>A (p.W1282*), c.3889dupT, c.3909C>G (p.N1303K).

Spinal muscular atrophy: The copy number of *SMN1* exon 7 is assessed relative to internal standard reference genes by quantitative polymerase chain reaction (qPCR). A mathematical algorithm calculates 0, 1, 2 and 3 copies with statistical confidence. When no copies of *SMN1* are detected, the primer and probe binding sites are sequenced to rule out variants that could interfere with copy number analysis and *SMN2* copy number is assessed by digital droplet PCR analysis relative to an internal standard reference gene. For carrier screening, when two copies of *SMN1* are detected, allelic discrimination qPCR targeting c.*3+80T>G in *SMN1* is performed.

Fragile X syndrome: DNA is amplified by the polymerase chain reaction (PCR) to determine the size of the CGG repeat region within the *FMR1* gene. PCR products are generated using a fluorescence labeled primer and sized by capillary gel electrophoresis. If indicated, Southern blot analysis is performed by hybridizing the probe StB12.3 to EcoRI- and EagI-digested DNA. The analytical sensitivity of both Southern blot and PCR analyses is 99% for expansion mutations in the *FMR1* gene. Reported CGG repeat sizes may vary as follows: +/- one for repeats less than 60, and +/- two to four for repeats in the 60 - 120 range. For repeats greater than 120, the accuracy is +/- 10%. If 55-90 trinucleotide repeats are detected in females (excluding prenatal specimens), a PCR assay targeting AGG sequences within the CGG repeats is performed to assess the number and position of AGG interruptions.

Limitations: False positive or false negative results may occur for reasons that include genetic variants, blood transfusions, bone marrow transplantation, somatic or tissue-specific mosaicism, mislabeled samples, or erroneous representation of family relationships.

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INFORMATION TABLES

CF risk reductions for individuals with no family history				
Disorder *(Gene)* Reference Sequence	**Population**	**Detection rate**	**Pre-test carrier risk**	**Post-test carrier risk with negative result**
Cystic fibrosis *(CFTR)* NM_000492	African American	81%	1 in 61	1 in 316
	Ashkenazi Jewish	97%	1 in 24	1 in 767
	Asian American	55%	1 in 94	1 in 208
	Caucasian	93%	1 in 25	1 in 343
	Hispanic	78%	1 in 58	1 in 260
	Mixed or other ethnic background	For counseling purposes, consider using the ethnic background with the most conservative risk estimates.		

SMA risk reductions for individuals with no family history						
Disorder *(Gene)* Reference Sequence	**Population**	**Detection rate (Copy number + SNP)**	**Pre-test carrier risk**	**Post-test risk of being a carrier with 2 copies****		**Post-test risk of being a carrier with 3 copies**
				POSITIVE for the c.*3+80T>G SNP	**NEGATIVE for the c.*3+80T>G SNP**	
Spinal muscular atrophy *(SMN1)* NM_000344	African American	90.3%	1 in 72	1 in 34	1 in 375	1 in 4200
	Ashkenazi Jewish	92.8%	1 in 67	High risk	1 in 918	1 in 5400
	Asian	93.6%	1 in 59	High risk	1 in 907	1 in 5600
	Caucasian	95.0%	1 in 47	1 in 29	1 in 921	1 in 5600
	Hispanic	92.6%	1 in 68	1 in 140	1 in 906	1 in 5400
	Mixed or other ethnic background	For counseling purposes, consider using the ethnic background with the most conservative risk estimates.				

** includes carriers who are silent carriers (2+0) and carriers with a pathogenic variant not detected in this assay
Feng, PMID 28125085; Luo, PMID 23788250; Sugarman, PMID 21811307

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