

QHerit[™] Expanded Carrier Screen

Test Code: 94372 (X)

Specimen Requirements: Preferred: 6 mL (4 mL minimum) room-temperature whole blood: 1.5 mL (1 mL minimum) in each of 4 lavender-top (EDTA) or yellow-top (ACD) tubes

Alternatives: 10 to 15 mL room-temperature amniotic fluid (sterile plastic container) or 10 to 20 mg chorionic villi in 2 to 3 mL sterile saline or tissue culture medium (sterile plastic container)

Note: The QHerit[™] Expanded Carrier Screen may not be ordered on fetal specimens. Fetal testing is available for each of the 22 individual diseases (ie, not as a panel).

CPT Codes*: 81200, 81205, 81209, 81220, 81242, 81243, 81250, 81251, 81255, 81257, 81260, 81290, 81330, 81400 (x4), 81401 (x3), 81479

CLINICAL USE

• Determine carrier risk for 22 clinically actionable, heritable diseases

CLINICAL BACKGROUND

Mendelian disorders occur before 25 years of age in an estimated 0.4% of live births.¹ Preconception and prenatal screening can identify carriers of genetic variants that cause these disorders and, thus, help couples plan and manage their pregnancies.

Carrier screening has traditionally targeted ethnicities that are at higher risk of disorders. An ethnicity-based approach presents difficulties for individuals who are multi-racial, adopted, or have incomplete or incorrect information about their ethnic backgrounds. This difficulty, combined with the advent of next-generation sequencing (NGS), has led to consideration of screening individuals regardless of ethnicity.

NGS has improved sequencing costs and efficiency, enabling the creation of expanded carrier screening (ECS) panels. These panels allow testing of many disorders at once and may improve outcomes and cost-effectiveness compared to traditional screening.² Studies have also shown that ECS panels are clinically valid for carrier screening^{3,4} and have clinical utility for infertile or at-risk couples.^{5,6} The advantages of NGS have led to some published ECS panels that test for hundreds of conditions. This approach can lead to more than half of tested patients being identified as carriers,⁷ which can, in turn, lead to testing of partners and patient anxiety. Furthermore, testing for some conditions may not provide clinical utility (eg, conditions that have weak association with tested variants or are so rare that residual risk after a negative result is impossible to calculate).⁸ Thus, the conditions included on ECS panels should be carefully selected.

In March 2017, the American College of Obstetricians and Gynecologists (ACOG) released criteria for conditions included in ECS panels.⁷ The guidelines suggest that conditions meet "several" of the following criteria: 1) carrier frequency ≥1 in 100; 2) well-defined phenotype; 3) negative effect on quality of life; 4) cause of cognitive or physical disability; or 5) early onset. Furthermore, diagnosis before birth and disease treatment, management, or education should be possible.

In 2015, a joint statement about points to consider for ECS was also released by the following 5 medical organizations⁸: 1) the American College of Medical Genetics and Genomics (ACMG), 2) ACOG, 3) the National Society of Genetic Counselors (NSGC), 4) the Perinatal Quality Foundation, and 5) the Society for Maternal-Fetal Medicine (SMFM). The joint statement contains criteria that align with the 2017 ACOG guidelines. It also includes additional exclusion criteria. Specifically, conditions should not be included in ECS panels if: 1) testing cannot distinguish between adult and childhood onset; 2) associated alleles are relatively common in the general population but penetrance is low; or 3) other methods are more appropriate than molecular testing.

The QHerit Expanded Carrier Screen is consistent with the guidelines discussed above.^{7,8} The assay includes testing for clinically actionable variants in 24 genes related to 22 heritable diseases (**Table**) that are included in genetic testing guidelines from ACOG, ACMG, NSGC, or the Jewish Genetic Disease Consortium (JGDC).

INDIVIDUALS SUITABLE FOR TESTING

• Individuals of any ethnicity or geographic origin who are pregnant or considering pregnancy

Table. QHerit Expanded Carrier Screen: Tested Variants, Individual Tests, Related Guidelines, Detection Rates, and Residual Risk

Alpha-Thalassemia HBA1, HBA2	Disease	Tested Gene(s)	Tested Variant(s)
Beta-Hamoglobinopathies MBR Sale footnote b. Introducing Schede Cell Disease BLM 22010/01/01/02/2012/02/2016/02/04/02/04/04/04/04/04/04/04/04/04/04/04/04/04/	Alpha-Thalassemia	HBA1, HBA2	-alpha3.7, -alpha4.2, -alpha20.5,SEA,MED,FIL,THAI, Constant Spring (c.427T>C)
Bioom Syndrome PLM 2281de6/no7 (c.2207.212de1(ATCTGA)insTAGATTO) Canavan Disease A5PA NS2-240 (c.433-2A-0) (X3TX (c.683C)A), E286A (c.854A)C), A30E (c.914C)A) Cystic Fibrosis CFTR See footnote d. Dihydrolipoamide Dehydrogenase Deficiency D(D) Y35* (c.104dupA), 6229C (c.885601) Familial Dysoutonomia NCKAP R96P (c.20970-C), NS20+6T-C (c.2204+6T-C) Familial Dysoutonomia ABCCS NS32+390-A (c.3989-80-A), F18374-16 (c.400-C) Familial Dysoutonomia NS4+A37-C (c.406+A471), 3224e8 (c.6724e10-C) Referee Fraglic X Syndrome FMR1 CGG tripit repat number is reported NS2+400-C (c.8300-C), 2275C (c.8302-T) Gaucher Disease GBP R560 (c.2470-C), Q47X (c.10302-T) L342P (c.1442D-C), L442P (c.1442D-C), L42P (c.1442D-C), L42P (c.1442D-C	Beta-Hemoglobinopathies (Including Sickle Cell Disease)	HBB	See footnote b.
Canavan Disoase ASPA INS2-24-Xi (C.433-24-Xi) (X.435-24-Xi), E.633C-Xi), E285A (C.554-Xi), A305E (C.314C)Xi) Cystic Fibrosis CFTR See footnote d. Dihydrol[poarnide Dehydrogenase Deficiency DLD Y35* (C.104 dupA), G229C (C.6856671) Familial Dysautonomia MBKAP R666P (C.20070-C), INS20-6FD (C.2204+6FD C) Familial Dysautonomia MBKAP R666P (C.20070-C), INS20-6FD (C.2204+6FD C) Familial Dysautonomia MBCCR INS2-463-K: 0.3989-36X, J.F1387/del (C.4160, C.10264/TCT) Familial Type in Sulfinam ABCCR INS2-463-K: 0.3989-36X, J.F1387/del (C.4160, C.10264/TCT) Familial Type in Sulfinam ABCCR INS2-463-K: 0.3989-36X, J.F1387/del (C.4160, C.4162/delTCT) Familial Type in Sulfinam ABCCR INS2-463-K: 0.3989-36X, J.F1387/del (C.4160, C.4162/delTCT) Familial Type in Sulfinam ABCCR INS2-463-K: 0.3989-36X, J.F1387/del (C.4160, C.4102/delTCT) Familial Type in Sulfinam FMR1 CGG triplet repeat number is reported Gaucher Disease GRA repeat 103/del (C.41430), R460 (C.144302), R460 (Bloom Syndrome	BLM	2281del6/ins7 (c.2207_2212del(ATCTGA)insTAGATTC)
Cystic Fibrosis CFTR See footnote d. Dihydrolipoamide Dehydrogenase Deficiency DLD V36* (c.104dupA), 6229C (c.68565T) Familial Dysautonomia IRBKAP R998P (c.20970x0), IV520+61xC (c.2204+61xC) Familial Hyperinsulmism ABCC8 IV532-905A (c.5989-905A), F13874el (c.4180, 4182, 4120	Canavan Disease	ASPA	IVS2-2A>G (c.433-2A>G), Y231X (c.693C>A), E285A (c.854A>C), A305E (c.914C>A)
Dihydrolipoamide Dehydrogenase Deficiency DLD Y35* (c.104dupA), G229C (c.685G)T) Familial Dysautonomia KBKAP R896P (c.20870-C), IVS20+6DC (c.2204+6D-C) Familial Dyseninsutniam ABCC8 IVS32-9GA (c.3898-9GA), F1387del (c.4160_4182delTCT) Fansoni Anemia Type C FANCC IVS32-9GA (c.458-4APT), 322delG (c.67delG) Fragile X Syndrome FMR1 CGG triplet repeat number is reported Gaucher Disease OBA del55bp (c.1283_1317del5b), V394 (c.1297G)T), D409H (c.13420-C), L444P (c.1445D-C), R469H (c.1604G5A) Glycogen Storage Disease Type IA G6PC R83C (c.247C>T), Q347X (c.1039C>T) Joubert Syndrome 2 TMEM216 R731 (c.21863T) Mucolipidosis IV MCOL N11 IVS3-2ASG (c.406-7ASG), 6.44b-del (g.7586622-7583055del) Nemaline Myopathy NEB 2502bp del (c.74317H171_7536+377del) Nemaline Myopathy NEB 2502bp del (c.74317H171_7536+377del) Nemaline Myopathy NEB 2502bp del (c.74317H171_7536+377del) Nemann-Pick Disease Types A and B SMP01 L302P (c.9117D, f.5P330 (c.996delC), R249W (c.745C>T) Tay-Sachs Disease HEXA SMN1 and SMN2 copy numbers are reported Spinal Muscular Atro	Cystic Fibrosis	CFTR	See footnote d.
Familial Dysautonomia MBKAP R696P (c.20870x0, IVS20+6TxC (c.2204+6TxC)) Familial Hyperinsulinism ABCC8 IVS32-9GxA, c.3389-9GxA), F1387del (c.4160, 4162delTCT) Fanconi Anemia Type C FANOC IVS4+4A31 (c.456+4A31), 322delG (c.67delG) Fraglie X Syndrome FMR1 CCG triplet repeat number is reported Gaucher Disease GBA (dl55bp (c.126, 317del5b), V3941 (c.1279G3T), D409H (c.1342G5C), L444P (c.1448TbC), R496H (c.1604G3A) Glycogen Storage Disease Type IA G6PC R83C (c.247CxT), 0347X (c.1039CxT) Joubert Syndrome 2 TMEM216 R73L (c.218G3T) Mucolipidosis IV MCOLN1 IVS2-2A3C (c.406-2A3C), 6.44b, del (g.7586622, 7593055del) Nemaine Myopathy NEB 2502bp del (c.7431+1917, 7536+372del) Niemann-Pick Disease Types A and B SMPD1 L302P (c.311TbC), fsP330 (c.980dcC), R490H (c.1493G5T), deltaR606 (c.1823, 1831delGCC) Spinal Muscular Atrophy SMN1, SMN2 SMN1 and SMN2 copy numbers are reported Fay-Sachs Disease HEXA Pseudodeficiency variants: R247W (c.738C5T), R249W (c.745C5T), 0174+1072, 1739+1072 (c.11274, 127740pT4C), 1727+1074 (c.3132A), 1278147C (c.1322-127340pT4C), 1752+1022 (c.1421+162C), 7580-432-491 Usber Syndrome Type IIF PCDH15 R245+(c.733C5T), 023+10520, 12728147C (c.1274-127740pT4C), 1752+1022 (c.1421+162C), 768b, del, Ex1 (c.2564, 263+5128delinsG) Usber Syndrome Type IIIA CLRM1 N446K (c.14476), 03<	Dihydrolipoamide Dehydrogenase Deficiency	DLD	Y35* (c.104dupA), G229C (c.685G>T)
Familial Hyperinsulinism ABCC8 IVS32-9G>A (c.3889-9G>A), F1387del (c.4160_4162/delTCT) Fanconi Anemia Type C FANCC IVS4+4A3T (c.456+4A3T), 322del3 (c.62del3) Fraglie X Syndrome FMR1 CGG triplet repeat number is reported Gaucher Disease IVS2+1G>A (c.111+1G>A), 840G (c.82del30, N3705 (c.1226A>0), del55bp (c.1283_1137del55A), 0394L (c.12975T), 0409H (c.13425>C), L444P (c.14481>C), R498H (c.1604G>A) Glycogen Storage Disease Type IA G6PC R83C (c.247C>T), 0347X (c.1039C>T) Joubert Syndrome 2 TMEM216 R73L (c.218G>T) Maple Synup Urine Disease BCKDHA R183P (c.5486>C), G278S (c.832G>A), E372X (c.1114G>T) Mucolipidosis IV MCOLVI IVS3-2A>G (c.406-2A>G), 6.446, del (g.7586622, 7593055del) Nemaline Myopathy NEB Z502b pd (c.7341+917_7536+372del) Nemaline Myopathy NEB SMPD1 L302P (c.311T>C), fs9330 (c.986delC), R498L (c.1493G>T), deltaR608 (c.1829_1831delGCC) Spinal Muscular Atrophy SMN1, SMN2 SMN1 and SMN2 copy numbers are reported Tay-Sachs Disease HEXA Disease Interval (c.733CA), 1278TATC (c.1274_1277)dp1ATC), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277)dp1ATC), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277)dp1ATC), IVS12+1G>C), 7.645-1c33CA), 26695 (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277)dp1ATC), IVS12+1G>C (c.421+1G>C), 7.645-1c61, Ex1 (c.2564_253+5128delinsG) Usher Syndrome Type III CLRN1 NA4K (c.1447)G) </td <td> Familial Dysautonomia</td> <td>IKBKAP</td> <td>R696P (c.2087G>C), IVS20+6T>C (c.2204+6T>C)</td>	 Familial Dysautonomia	IKBKAP	R696P (c.2087G>C), IVS20+6T>C (c.2204+6T>C)
Fanconi Anemia Type CFANOCIVS4+4A>T (c.456+4A>T), 322del(G (c.67delG)Fragile X SyndromeFMR1CGG triplet repeat number is reportedGaucher DiseaseGBAdel55b (c.128, 1317del55), V3944, (c.1297o)T), D409H (c.1342G>C), L444P (c.1448T>C), R499H (c.1604G)A)Glycogen Storage Disease Type IAG6PCR83C (c.247C>T), 0347X (c.1039C>T)Joubert Syndrome 2TMEM218R73L (c.21863T)Maple Syrup Urine DiseaseBCKDHAR183P (c.5486C>C), 0278 (c.832G>A), E372X (c.1114G)T)Musculpidosis IVMCOLNIIVS3-2A>G (c.406-2A>G), 6, 44b, del (g.7586622, 7593055del)Nemaline MyopathyNEB2502bp del (c.7431+1917, 2536+372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996delC), R49EL (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C)T), R249W (c.745C)T) Other variants: R178H/B1 variant (c.533G>A), G2695 (c.805G>A), IVS9+1G>A(c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12160>C (c.1421+16)C), 7.845L (d.147-16)Usher Syndrome Type IFPCDH15R245 (c.738C)T IVS9+1G>A(c.1734+1G)A, 1278TATC (c.1274_1277dupTATC), IVS12160>C (c.1421+16)C), 7.845L (d.147-16)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Familial Hyperinsulinism	ABCC8	IVS32-9G>A (c.3989-9G>A), F1387del (c.4160_4162delTCT)
Fragile X SyndromeFMR1CGG triplet repeat number is reportedGaucher DiseaseGBAIVS2+1G>A (c.115+1G>A), 84GG (c.84dupG), N370S (c.1226A>G), de155bp (c.1263_1317de155), V394L (c.1297G>T), D409H (c.1342G>C), L444P (c.144B1>C), R496H (c.1604G>A)Glycogen Storage Disease Type IAG6PCR83C (c.247C>T), Q347X (c.1039C>T)Joubert Syndrome 2TMEM216R73L (c.218G>T)Maple Syrup Urine DiseaseBCKDHAR183P (c.548G>C), G278S (c.832G>A), E372X (c.1114G>T)Mucolipidosis IVMCOLN1IVS3-2A>G (c.406-2A>G), 6.44b_dei (g.7586622, 7593055dei)Nemaline MyopathyNEB2502bp dei (c.7431+1917_7536+372dei)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996deiC), R496L (c.1493G>T), de1taR608 (c.1829_1831deIGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.733C>T), R249W (c.745C>T) Uther variantes: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS1+16>C (c.1421+1G>C), 7.6kb_dei, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245F (c.733C>T) R245F (c.733C>T)Usher Syndrome Type IIIACLRNI<	Fanconi Anemia Type C	FANCC	IVS4+4A>T (c.456+4A>T), 322delG (c.67delG)
Gaucher Disease GBA IVS2+1G>A (c.115+1G>A), 84GG (c.84dupG), N370S (c.1226A>G), 4el55bp (c.1283_1317del55), V394L (c.1297G>T), D409H (c.1342G>C), L444P (c.1448T>C), R496H (c.1604G>A) Glycogen Storage Disease Type IA G6PC R83C (c.247CT), 0347X (c.1039C)T Joubert Syndrome 2 TMEM216 R73L (c.218G>T) Maple Syrup Urine Disease BCKDHA R183P (c.548G>C), 6278S (c.832G>A), E372X (c.1114G>T) Mucolipidosis IV MCOLN1 IVS3-2A>G (c.406-2A>G), 6.4kb_del (g.7586632_7593055del) Nemaline Myopathy NEB 2502bp del (c.7431+1917, 7536+372del) Niemann-Pick Disease Types A and B SMPD1 L302P (c.311T)C), fsP330 (c.396delC), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC) Spinal Muscular Atrophy SMN1, SMN2 SMN1 and SMN2 copy numbers are reported Tay-Sachs Disease HEXA Pseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+16>C (c.1274_1277dupTATC), IVS12+16>C (c.1274_110>C), 76kb_del, Ex1 (c.2564_253+5128delinsG) Usher Syndrome Type IF PCDH15 R245F (c.733C>T) Usher Syndrome Type IIIA CLRN1 N48K (c.1447bG) Maker-Warburg Syndrome FKTN F3907s (c.1167dupA) E3907s (c.1167dupA) E3907s (c.1167dupA) E3907s (c.1167dupA) E3907s (c.1167dupA)	Fragile X Syndrome	FMR1	CGG triplet repeat number is reported
Gaucher DiseaseGBAdel55bp (c.1263_1317del55), V394L (c.1297G>T), D409H (c.1342G>C), L444P (c.144BT>C), R496H (c.1604G>A)Glycogen Storage Disease Type IAG6PCR83C (c.247C>T), 0347X (c.1039C>T)Joubert Syndrome 2TMEM216R73L (c.218G>T)Maple Syrup Urine DiseaseBCKDHAR183P (c.548G>C), G278S (c.832G>A), E372X (c.1114G>T)Mucolipidosis IVMCOLN1IV53-2A>G (c.406-2A>G), 64Kb, del (g.7586622_7593055del)Nemaline MyopathyNEB2502bp del (c.7431+1917_75364-372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996del(C), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), 0269S (c.805G>A), IV59+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IV51+1G>C (c.1441+G), 744AF (G), 744AF (G		•••••	IVS2+1G>A (c.115+1G>A), 84GG (c.84dupG), N370S (c.1226A>G),
Glycogen Storage Disease Type IA G6PC R83C (c.247CxT), 0347X (c.1039CxT) Joubert Syndrome 2 TMEM216 R73L (c.218GxT) Maple Syrup Urine Disease BCKDHA R183P (c.548Gx)C), 0278S (c.832GxA), E372X (c.1114GxT) Mucolipidosis IV MCOLN1 IVS3-2AxG (c.406-2AxG), 6.4kb_del (g.7586622_7593055del) Nemaline Myopathy NEB 2502bp del (c.7431+1917_7536+372del) Niemann-Pick Disease Types A and B SMPD1 L302P (c.911TxC), fsP330 (c.996delC), R496L (c.1493GxT), deltaR608 (c.1829_1831delGCC) Spinal Muscular Atrophy SMN1, SMN2 SMN1 and SMN2 copy numbers are reported Tay-Sachs Disease HEXA Pseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533GxA), 0269S (c.805GxA), IVS9+1GxA (c.1073+1GxA), 1278TATC (c.1274_1277dupTATC), IVS12+1GxC (c.1073+1GxA), 1278TATC (c.1274_1277dupTATC), IVS12+1GxC (c.1274_1277dupTATC), IVS12+1GxC (c.1274_127, 1277dupTATC), IVS12+1GxC (c.733C>T) Usher Syndrome Type IIF PCDH15 R245* (c.733C>T) Usher Syndrome Type IIIA CLRN1 N485* (c.1167dupA) Walker-Warburg Syndrome FKTN F390fs (c.1167dupA)	Gaucher Disease	GBA	del55bp (c.1263_1317del55), V394L (c.1297G>T), D409H (c.1342G>C),
Glycogen Storage Disease Type IAG6PCR83C (c.247C>T), 0347X (c.1039C>T)Joubert Syndrome 2TMEM216R73L (c.218G>T)Maple Syrup Urine DiseaseBCKDHAR183P (c.548G>C), 0278S (c.832G>A), E372X (c.1114G>T)Mucolipidosis IVMCOLN1IVS3-2A>G (c.406-2A>G), 6.4kb_del (g.7586622_7593055del)Nematine MyopathyNEB2502bp del (c.7431+1917_7536+372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996delC), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G2695 (c.805G>A), IVS9+1GA (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R2454 (c.733C>T)Usher Syndrome Type IIACLRN1N48K (c.144T>G)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)		•••••	L444P (c.1448T>C), R496H (c.1604G>A)
Joubert Syndrome 2TMEM216R73L (c.218G)T)Maple Syrup Urine DiseaseBCKDHAR183P (c.548G)C), G278S (c.832G)A), E372X (c.1114G)T)Mucolipidosis IVMCOLN1IVS3-2A/G (c.406-2A/G), 6.4kb_del (g.7586622_7593055del)Nemaline MyopathyNEB2502bp del (c.7431+1917_7536+372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.9117)C), fsP330 (c.996delC), R496L (c.1493G)T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C)T), R249W (c.745C)T) Other variants: R178H/B1 variant (c.533G)A), G269S (c.805G)A), IVS9+1GA (c.1073+163A), 1278TATC (c.1274_1277dupTATC), IVS12140>C (c.1421+1G)C), 7.6kb_del, Ex1 (c.2664_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C)T) Usher Syndrome Type IIIAUsher Syndrome Type IIIACLRN1N48K (c.1147)-G) Y48K (c.1167dupA)	Glycogen Storage Disease Type IA	G6PC	R83C (c.247C>T), Q347X (c.1039C>T)
Maple Syrup Urine DiseaseBCKDHAR183P (c.548G>C), G278S (c.832G>A), E372X (c.1114G>T)Mucolipidosis IVMCOLN1IVS3-2A>G (c.406-2A>G), 6.4kb_del (g.7586622_7593055del)Nemaline MyopathyNEB2502bp del (c.7431+1917_7536+372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996delC), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ext (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T) Usher Syndrome Type IIIAUsher SyndromeFKTNF390fs (c.1167dupA)	Joubert Syndrome 2	TMEM216	R73L (c.218G>T)
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Nemaline MyopathyNEB2502bp del (c.7431+1917_7536+372del)Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996delC), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), 62695 (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T) Usher Syndrome Type IIIAWalker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Mucolipidosis IV	MCOLN1	IVS3-2A>G (c.406-2A>G), 6.4kb_del (g.7586622_7593055del)
Niemann-Pick Disease Types A and BSMPD1L302P (c.911T>C), fsP330 (c.996delC), R496L (c.1493G>T), deltaR608 (c.1829_1831delGCC)Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T) Usher Syndrome Type IIIAWalker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Nemaline Myopathy	NEB	2502bp del (c.7431+1917_7536+372del)
Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T)Usher Syndrome Type IIIACLRN1N48K (c.1147>G)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Niemann-Pick Disease Types A and B	SMPD1	L302P (c.911T>C), fsP330 (c.996delC), R496L (c.1493G>T),
Spinal Muscular AtrophySMN1, SMN2SMN1 and SMN2 copy numbers are reportedTay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T) Usher Syndrome Type IIIAUsher Syndrome Type IIIACLRN1N48K (c.144T>G) F390fs (c.1167dupA)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)			
Tay-Sachs DiseaseHEXAPseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)Usher Syndrome Type IFPCDH15R245* (c.733C>T)Usher Syndrome Type IIIACLRN1N48K (c.144T>G)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Spinal Muscular Atrophy	SMN1, SMN2	SMN1 and SMN2 copy numbers are reported
Usher Syndrome Type IFPCDH15R245* (c.733C>T)Usher Syndrome Type IIIACLRN1N48K (c.144T>G)Walker-Warburg SyndromeFKTNF390fs (c.1167dupA)	Tay-Sachs Disease	HEXA	Pseudodeficiency variants: R247W (c.739C>T), R249W (c.745C>T) Other variants: R178H/B1 variant (c.533G>A), G269S (c.805G>A), IVS9+1G>A (c.1073+1G>A), 1278TATC (c.1274_1277dupTATC), IVS12+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)
Usher Syndrome Type IIIA CLRN1 N48K (c.144T>G) Walker-Warburg Syndrome FKTN F390fs (c.1167dupA)	Usher Syndrome Type IF	PCDH15	R245* (c.733C>T)
Walker-Warburg Syndrome FKTN F390fs (c.1167dupA)	Usher Syndrome Type IIIA	CLRN1	N48K (c.144T>G)
	Walker-Warburg Syndrome	FKTN	F390fs (c.1167dupA)

ACMG indicates American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists; AJ, Ashkenazi Jewish; JGDC, Jewish Genetic Disease Consortium; NSGC, National Society of Genetic Counselors; SMFM, Society for Maternal-Fetal Medicine.

For footnotes, see Table Footnotes section in body text.

	Individual Test (Test Code)	Guidelines That Indicate Testing	Ethnicity or Sex
	Alpha-Globin Common Mutation Analysis (11175)ª	ACOG (per ancestry) ^{7,9}	Mediterranean, Middle Eastern, Southeast Asian, African, Chinese, Asian Indian
	Beta-Globin Complete (14974)°	ACOG (per ancestry) ^{7,9}	Mediterranean, Middle Eastern, Southeast Asian, African, Chinese, Asian Indian
• • • • • • • • • • • • •	Bloom Syndrome DNA Mutation Analysis (90872)	ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
• • • • • • • • • • • • •	Consumer Diseases Mutatian Analysis (0000E)		Ashkenazi Jewish
	Canavan Disease Mutation Analysis (90905)	ACOG (AJ) ^{7,9} , ACIVIG (AJ) ¹⁹ , JGDC ¹¹	Non-Ashkenazi Jewish
			Ashkenazi Jewish
		ACOG (all women) ^{7,9} ; ACMG	Non-Hispanic Caucasian
	CFvantage® CF Expanded Screen (92068)	(all women) ¹² ; NSGC (all women) ¹³ ;	Hispanic American
		JGDC ¹¹	African American
			Asian American
	Dihydrolipoamide Dehydrogenase Deficiency (DLD Deficiency) (92046)	JGDC (lipoaminde dehydrogenase deficiency [E3]) ¹¹	Ashkenazi Jewish
• • • • • • • • • • • • •	Familial Dysautonomia Mutation Analysis (90912)	ACOG (AJ) ⁹ ; ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
• • • • • • • • • • • • •	Familial Hyperinsulinism (92045)	JGDC ¹¹	Ashkenazi Jewish
••••••	Fanconi Anemia DNA Mutation Analysis (90897)	ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
	XSense®, Fragile X w/Reflex (16313)	ACOG (family history) ^{7,9} ; ACMG (family history) ¹⁴ ; NSGC (family history) ¹⁵	Females
	Gaucher Disease DNA Mutation Analysis (90907)	ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
••••••	Glycogen Storage Disease Type IA Mutation Analysis	JGDC ¹¹	Ashkenazi Jewish
• • • • • • • • • • • •	Joubert Syndrome 2 (92050)	.IGDC ¹¹	Ashkenazi.lewish
• • • • • • • • • • • •	Maple Syrup Urine Disease (MSUD) Mutation		
	Analysis (90909)	JGDC ¹¹	Ashkenazi Jewish
• • • • • • • • • • • •	Mucolipidosis IV Mutation Analysis (90899)	ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
• • • • • • • • • • • • •	Nemaline Myopathy (92055)	JGDC ¹¹	Ashkenazi Jewish
	Niemann-Pick Disease Mutation Analysis (90893)	ACMG (AJ) ¹⁰ ; JGDC ¹¹	Ashkenazi Jewish
	SMA Carrier Screen (18041)	$ACOC (f_{a})$ + biotor λ^{79} + ACNAC	Caucasian
		(all women) ¹⁶ : IGDC ¹¹	Ashkenazi Jewish
			Asian
			African American
			Hispanic
			Ashkenazi Jewish
	Tay-Sachs Disease Mutation Analysis (90903)	ACOG (AJ, Cajun, French Canadian) ^{7,9} ; ACMG (AJ) ¹⁰ ; JGDC ¹¹	French-Canadian
			General Population
	Usher Syndrome Type IF (92047)	JGDC ¹¹	Ashkenazi Jewish
	Usher Syndrome Type III (92048)	JGDC ¹¹	Ashkenazi Jewish
	Walker-Warburg Syndrome (92051)	JGDC ¹¹	Ashkenazi Jewish

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	Detection Rate, %	Prior Carrier Risk	Residual Risk After a N	egative Result	References for Rates and Risks
	Up to 94	Varies by ethnicity	Reduced		17
	99	Varies by ethnicity	Reduced		17 and footnote e
• • • • • • • • • • • • • • •	99	1/134	1/13,301	• • • • • • • • • • • • • • • • • • • •	18
••••••	>97	1/55	<1/1,801	• • • • • • • • • • • • • • • • • • • •	18
• • • • • • • • • • • • • • • • • • • •	50	Not known	••••••••••••••••••••••••••••••••••••	• • • • • • • • • • • • • • • • • • • •	19,20
• • • • • • • • • • • • • • • •	95	1/24	1/461		
• • • • • • • • • • • • • • • • • • • •	90	1/25	1/241		
• • • • • • • • • • • • • • • • • • • •	88	1/46	1/376		21-24
•••••••••••	78	1/65	1/292	••••••	
••••••	53	1/94	1/199	••••••	
	>95	1/107	<1/2,121		18,24
•••••••	<u>>99</u>	1/31	<1/3 001	•••••••••••••••••••••••••••••••••••••••	
••••••••••••	90	1/68	1/671	• • • • • • • • • • • • • • • • • • • •	18
• • • • • • • • • • • • • • • • • • • •	99	1/100	1/0 001	• • • • • • • • • • • • • • • • • • • •	18
•••••••		1/100	173,301	•••••••••••••••••••••••••••••••••••••••	10
	99	1/259	1/25,801		14,25,26
	95	1/15	1/281		18
• • • • • • • • • • • • • • • •	95	1/64	1/1,261		18
• • • • • • • • • • • • • • • • • • • •	51	1/177	1/360	• • • • • • • • • • • • • • • • • • • •	27
• • • • • • • • • • • • • • • • • • • •	99	1/107	1/10,601	• • • • • • • • • • • • • • • • • • • •	28
• • • • • • • • • • • • • •	95	1/97	1/1,921	•••••••••••••••••••••••••••••••••••••••	18
• • • • • • • • • • • • • • •	95	1/89	1/1.761	• • • • • • • • • • • • • • • • • • • •	18
••••••	>95	1/168	<1/3 341	• • • • • • • • • • • • • • • • • • • •	18
•••••••••••				• • • • • • • • • • • • • • • • • • • •	
	97	1/115	1/3,801		18
			2 SMN1	3 SMN1	
			copy result	copy result	
	95	1/35	1/632	1/3,500	
	90	1/41	1/350	1/4,000	29
	93	1/53	1/628	1/5,000	
	71	1/66	1/121	1/3,000	
• • • • • • • • • • • • • • • •	91	1/117	1/1,061	1/11,000	
· · · · · · · · · · · · · · · · ·	98	1/27	1/1,301		18
	70	1/31	1/101		30
	46	1/300	1/555		30
	>75	1/147	<1/585		18
	>95	1/120	<1/2,381		18
	99	1/79	1/7,801		28



METHOD

- Fragile X syndrome (FXS): PCR and capillary electrophoresis; detect CGG repeat number
- Spinal muscular atrophy (SMA): real-time, allele-specific PCR; determine copy number of *SMN1* and *SMN2*
- Cystic fibrosis (CF): targeted multiplex NGS for 161 CF variants, including the 23 common variants recommended by ACOG/ACMG
- All other diseases: multiplex PCR of specific regions of 20 genes related to 19 diseases; NGS analysis follows PCR

INTERPRETIVE INFORMATION

Residual risk after a negative result for each gene/condition can be found in the **Table**. Results should be interpreted in conjunction with other laboratory and clinical findings.

FXS: Individuals with <45 CGG repeats are considered negative for FXS, while those with 45 to 54 CGG repeats are considered to be gray-zone allele carriers. No FXS-associated phenotype is expected for individuals with negative or gray-zone allele carrier results. If an expanded allele (>85 CGG repeats) is detected, both CGG repeat number and hypermethylation status are reported. Premutation allele carriers (repeat lengths of 55–200) are at risk of FXSassociated syndromes. Individuals with full mutation (>200 CGG repeats) and hypermethylation are predicted to be affected by FXS.

The associated risk of having a child with a premutation or a full mutation depends on the gender and mutation status of the parent and the gender of the child. This assay does not detect other mutations (eg, deletions and point mutations) that disrupt the function of the *FMR1* gene or protein.

SMA: A result of 1 or 0 *SMN1* copies indicates that the individual carries a disease-related deletion. This assay detects the copy number of *SMN1* and *SMN2*. This test cannot detect other pathogenic variants, nor can it identify silent carriers: individuals who have 2 or more copies of the

SMN1 gene on 1 chromosome and 0 copies of the *SMN1* gene on the opposite chromosome (eg, 2+0 carriers). The risk for pathogenic variants that cause SMA other than the deletions tested depends greatly on family history and clinical presentation. Therefore, if both members of a couple carry SMA deletions (with results indicating 1 or 0 copies of *SMN1* detected), or other pathogenic variants not detected by this assay, their children have a higher chance to be affected with SMA. This risk is 25% if both members of a couple each carry 1 *SMN1* deletion or other pathogenic variant.

All other genes/conditions: A positive result indicates that the individual carries a disease-related variant. Thus, the individual has an increased risk of having a child affected with the corresponding disease; testing of reproductive partners should be considered. If both members of a couple are carriers, their offspring have a 25% risk of being affected. The test report also indicates whether an individual has 1 copy of a pathogenic variant (carrier), 2 copies of the same variant (affected), or 1 copy each of 2 different variants (affected).

Additional assistance with interpretation of results is available for healthcare providers from our Genetic Counselors by calling Quest Genomics Client Services at 1.866.GENE.INFO (1.866.436.3463).

Visit QHerit.com/Clinicalinfo for additional clinical information and references.

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(continued on next page)

Table footnotes

^a QHerit Expanded Carrier Screen includes Hb Constant Spring, whereas the Alpha Globin Common Mutation Analysis test (test code 11175) does not.

HBB variants tested (including sickle cell disease and beta thalassemias): c.*111A>G, c.*110T>C, c.*96T>C, Hb D-Los Angeles (c.364G>C), Hb O-Arab (c.364G>A), c.321_322insG, c.316-2A>C, c.316-2A>G, c.316-3C>A, c.316-106C>G, c.316-125A>G, c.316-146T>G, c.316-197C>T, c.315+1G>A, c.287_288insA, c.251delG, c.230delC, c.216_217insA, c.203_204delTG, c.143_144insA, c.146_147insATCT, c.135delC, c.130G>T, c.126_129delCTTT, c.124_127delTTCT, c.118C>T, c.114G>A, c.112delT, c.93-1G>C, c.93-1G>A, c.93-21G>A, c.92+6T>C, c.92+5G>A, c.92+5G>C, c.92+5G>T, c.92+2T>A, c.92+2T>C, c.92+1G>A, c.92+1G>T, Hb Monroe (c.92G>C), c.92G>A, c.84_85insC, c.79G>T, HBE (c.79G>A), c.75T>A, c.59A>G, c.52A>T (LYS17*), c.51delC, c.48G>A, c.47G>A (Trp15), c.46delT, c.36delT, c.33C>A, c.27_28insG, c.25_26delAA, c.20delA, HBS (c.20A>T), HBC (c.19G>A), c.17_18delCT, c.2T>C, c.2T>G, c.1A>G, c.-78A>C, c.-78A>G, c.-79A>G, c.-80T>A, c.-81A>G, c.-136C>G, c.-137C>A, c.-137C>G, c.-137C>T, c.-138C>T, c.-138C>A, c.-140C>T, c.-151C>T.

° QHerit Expanded Carrier Screen does not include full sequencing, whereas the Beta-Globin Complete test (test code 14974) does.

 ${}^{\rm d}\,{\rm For}\,{\it CFTR}\,{\rm variants}\,{\rm tested}, {\rm see}\,{\rm online}: {\rm QuestDiagnostics.com/testcenter/testguide.action?dc=TS_QHerit.}$

^e Based on Quest Diagnostics samples tested 2004-2016.



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