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 organizations[8]: 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

Disease	Tested Gene(s)	Tested Variant(s)
Alpha-Thalassemia	*HBA1, HBA2*	-alpha3.7, -alpha4.2, -alpha20.5, --SEA, --MED, --FIL, --THAI, Constant Spring (c.427T>C)
Beta-Hemoglobinopathies (Including Sickle Cell Disease)	*HBB*	See footnote b.
Bloom Syndrome	*BLM*	2281del6/ins7 (c.2207_2212del(ATCTGA)insTAGATTC)
Canavan Disease	*ASPA*	IVS2-2A>G (c.433-2A>G), Y231X (c.693C>A), E285A (c.854A>C), A305E (c.914C>A)
Cystic Fibrosis	*CFTR*	See footnote d.
Dihydrolipoamide Dehydrogenase Deficiency	*DLD*	Y35* (c.104dupA), G229C (c.685G>T)
Familial Dysautonomia	*IKBKAP*	R696P (c.2087G>C), IVS20+6T>C (c.2204+6T>C)
Familial Hyperinsulinism	*ABCC8*	IVS32-9G>A (c.3989-9G>A), F1387del (c.4160_4162delTCT)
Fanconi Anemia Type C	*FANCC*	IVS4+4A>T (c.456+4A>T), 322delG (c.67delG)
Fragile X Syndrome	*FMR1*	CGG triplet repeat number is reported
Gaucher Disease	*GBA*	IVS2+1G>A (c.115+1G>A), 84GG (c.84dupG), N370S (c.1226A>G), del55bp (c.1263_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.247C>T), Q347X (c.1039C>T)
Joubert Syndrome 2	*TMEM216*	R73L (c.218G>T)
Maple Syrup Urine Disease	*BCKDHA*	R183P (c.548G>C), G278S (c.832G>A), E372X (c.1114G>T)
Mucolipidosis IV	*MCOLN1*	IVS3-2A>G (c.406-2A>G), 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.911T>C), fsP330 (c.996delC), 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+1G>C (c.1421+1G>C), 7.6kb_del, Ex1 (c.2564_253+5128delinsG)
Usher Syndrome Type IF	*PCDH15*	R245* (c.733C>T)
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)[c]	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
Canavan Disease Mutation Analysis (90905)	ACOG (AJ)[7,9]; ACMG (AJ)[10]; JGDC[11]	Ashkenazi Jewish
		Non-Ashkenazi Jewish
CFvantage® CF Expanded Screen (92068)	ACOG (all women)[7,9]; ACMG (all women)[12]; NSGC (all women)[13]; JGDC[11]	Ashkenazi Jewish
		Non-Hispanic Caucasian
		Hispanic American
		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 (90915)	JGDC[11]	Ashkenazi Jewish
		Caucasian
Joubert Syndrome 2 (92050)	JGDC[11]	Ashkenazi Jewish
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)	ACOG (family history)[7,9]; ACMG (all women)[16]; JGDC[11]	Caucasian
		Ashkenazi Jewish
		Asian
		African American
		Hispanic
Tay-Sachs Disease Mutation Analysis (90903)	ACOG (AJ, Cajun, French Canadian)[7,9]; ACMG (AJ)[10]; JGDC[11]	Ashkenazi Jewish
		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

Detection Rate, %	Prior Carrier Risk	Residual Risk After a Negative 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		21-24
90	1/25	1/241		
88	1/46	1/376		
78	1/65	1/292		
53	1/94	1/199		
>95	1/107	<1/2,121		18,24
>99	1/31	<1/3,001		18
90	1/68	1/671		18
99	1/100	1/9,901		18
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 copy result	*3 SMN1* copy result	29
95	1/35	1/632	1/3,500	
90	1/41	1/350	1/4,000	
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 FXS-associated 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.

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.

[b] *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.

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

[d] For *CFTR* variants tested, see online: QuestDiagnostics.com/testcenter/testguide.action?dc=TS_QHerit.

[e] Based on Quest Diagnostics samples tested 2004-2016.

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