Prenatal and Expanded Carrier Screening Panels

Indications for Ordering

Preconception and prenatal carrier screening for individuals or couples in the general population

Test Description

Targeted variant panels
- Polymerase chain reaction (PCR) and sequence-specific oligonucleotide probe hybridization

Next generation sequencing (NGS) panels
- Massively parallel sequencing and PCR

Fragile X screening
- PCR and capillary electrophoresis

Testing performed at Counsyl

Tests to Consider

Testing strategy
- Test one partner using the targeted variant panel
  - If positive, test the other partner using
    - Targeted variant panel, or
    - NGS panel, or
    - Sequencing of relevant gene(s) only
- Test one partner using the NGS panel
  - If positive, test the other partner using
    - NGS panel or
    - Sequencing of relevant gene(s) only
- Test both partners simultaneously, using
  - Targeted variant panel or
  - NGS panel
- Prenatal vs expanded panels
  - Prenatal panels are designed for parents of an ongoing pregnancy
    - Included disorders are considered severe
    - Fetal testing is available in the U.S.
  - Expanded panels include additional disorders and are intended for preconception carrier screening (before a pregnancy)
    - Some disorders are not considered severe
    - Fetal testing is not available for all disorders

Primary tests

85 disorders (prenatal carrier screening)
- Includes disorders that are considered severe and for which fetal testing is available in the U.S. (see Table 1)
- Prenatal Carrier Screening Targeted Mutation Panel, 85 Disorders 2007539
- Prenatal Carrier Screening Targeted Mutation Panel, 85 Disorders with Fragile X 2007541
- Prenatal Carrier Screening Panel by Next Generation Sequencing 2013849
- Prenatal Carrier Screening Next Generation Sequencing, 85 Disorders with Fragile X 2008704

100-plus disorders (preconception carrier screening)
- Includes disorders in Table 1 and additional disorders that may be considered nonsevere or for which fetal testing may not be available in the U.S. (see Table 2)
- Expanded Carrier Screening Panel Targeted Mutation, 100-Plus Disorders 2007543
- Expanded Carrier Screening Panel Targeted Mutation, 100-Plus Disorders with Fragile X 2007531
- Expanded Carrier Screening Next Generation Sequencing 2014000
- Expanded Carrier Screening Next Generation Sequencing, 100-Plus Disorders with Fragile X 2008701

Related tests
- Stand-alone carrier testing for some of the disorders on these panels is available at ARUP
- For couples in which an individual has been determined to be a carrier, gene sequencing for the partner may be available at ARUP
- For test availability and further information, please see test directory at ARUP Genetics

Disease Overview

Carrier screening
- Screening is important because recessive genetic disorders, collectively, are a relatively common cause of disease
- Carrier screening helps identify individuals and/or couples at risk for having children with a genetic disorder that is inherited in a manner that is
  - Autosomal recessive
  - X-linked

- Carrier rates vary by disorder and ethnicity
- Knowledge of carrier status can aid in making reproductive decisions before and during pregnancy
- Couples identified as carriers of the same disorder may elect to pursue
  - In vitro fertilization
  - Preimplantation genetic diagnosis
  - Prenatal diagnostic testing for the disorder

Disorders

See tables below

Genetics

Genes – a complete list of genes/variants tested will be included in the report

Inheritance

- Autosomal recessive
- X-linked

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - Depends on the disorder and the ethnicity of the individual
  - Will be included in report, if known
- Analytical sensitivity/specificity – > 99%

Results

- **Positive**
  - One gene variant detected
    - Individual is a carrier of the specified disorder(s)
      - Carriers usually do not experience symptoms of the disease
  - Two disease-causing variants detected
    - Homozygote or compound heterozygote
    - If located on opposite chromosomes
      - Individual is affected now or may be affected in the future with the specified disorder
- **Negative** – no targeted gene variants identified
  - Reduced carrier risk for tested disorders
- **Inconclusive –** unable to confidently report a positive or a negative result

Limitations

- Targeted variants panel
  - Determines only the specific variants included on the panel
- NGS testing
  - Reports only clinically significant variants
  - Variants of unknown significance, known benign variants, and likely benign variants are not reported
- Negative result does not exclude carrier status for these disorders
- Should not be ordered for the purpose of diagnostic testing in a symptomatic individual
- These panels will not detect chromosomal aneuploidy
- Should not be used in place of routine ultrasound or prenatal screening/diagnostic testing

Table 1

85 Disorders				
21-hydroxylase-deficient congenital adrenal hyperplasia*	*CLN5*-related neuronal ceroid lipofuscinosis	Glycogen storage disease type III	Lipoamide dehydrogenase deficiency	*PPT1*-related neuronal ceroid lipofuscinosis
ABCC8-related hyperinsulinism	Cohen syndrome	Gracile syndrome	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	Primary carnitine deficiency
Alpha-mannosidosis	Congenital disorder of glycosylation type Ib	Hereditary fructose intolerance	Medium-chain acyl-CoA dehydrogenase deficiency	Rhizomelic chondrodysplasia punctata type 1
Alpha-thalassemia*	Congenital disorder of glycosylation type Ia	Hb beta chain-related hemoglobinopathy (includes sickle cell disease)	Maple syrup urine disease type 1B	*PROP1*-related combined pituitary hormone deficiency
Ataxia-telangiectasia	Congenital Finnish nephrosis	Herlitz junctional epidermolysis bullosa, *LAMA3*-related	Megalencephalic leukoencephalopathy with subcortical cysts	Segawa syndrome
Autosomal recessive polycystic kidney disease	Costeff optic atrophy syndrome	Herlitz junctional epidermolysis bullosa, *LAMB3*-related	Metachromatic leukodystrophy	Short chain acyl-CoA dehydrogenase deficiency
Bardet-Beidl syndrome, *BBS1*-related	Cystic fibrosis	Herlitz junctional epidermolysis bullosa, *LAMC2*-related	Mucolipidosis IV	Sjögren-Larsson syndrome
Bardet-Biedl syndrome, *BBS10*-related	D-bifunctional protein deficiency	Hexosaminidase A deficiency (includes Tay-Sachs disease)	Muscle-eye-brain disease	Smith-Lemli-Opitz syndrome

85 Disorders				
Beta thalassemia	Familial dysautonomia	Homocystinuria caused by cystathionine beta-synthase deficiency	NEB-related nemaline myopathy	Spinal muscular atrophy
Biotinidase deficiency	Familial Mediterranean fever	Hurler syndrome	Niemann-Pick disease, *SMPD1*-associated	Steroid-resistant nephrotic syndrome
Bloom syndrome	Fanconi anemia type C	Hypophosphatasia, autosomal recessive	Nijmegen breakage syndrome	Sulfate transporter-related osteochondrodysplasia
Canavan disease	Galactosemia	Inclusion body myopathy 2	Northern epilepsy	*TPP1*-related neuronal ceroid lipofuscinosis
Carnitine palmitoyltransferase IA deficiency	Gaucher disease	Isovaleric acidemia	Pendred syndrome	Tyrosinemia type I
Carnitine palmitoyltransferase II deficiency	*GJB2*-related DFNB1 nonsyndromic hearing loss and deafness	Joubert syndrome 2	*PEX1*-related Zellweger spectrum disorder	Usher syndrome type 1F
Cartilage-hair hypoplasia	Glutaric acidemia type 1	Krabbe disease	Phenylalanine hydroxylase deficiency	Usher syndrome type 3
Citrullinemia type 1	Glycogen storage disease type Ia	Limb-girdle muscular dystrophy type 2D	Polyglandular autoimmune syndrome type 1	Very long-chain acyl-CoA dehydrogenase deficiency
CLN3-related neuronal ceroid lipofuscinosis	Glycogen storage disease type Ib	Limb-girdle muscular dystrophy type 2E	Pompe disease	Wilson disease
*Denotes disorders only included on the next generation sequencing versions of this test				

Table 2

100-Plus Disorders (in addition to 85 disorders in Table 1)		
Achromatopsia	Choroideremia	Primary hyperoxaluria type 1
Alkaptonuria	Cystinosis	Primary hyperoxaluria type 2
Alpha-1 antitrypsin deficiency	Factor XI deficiency	Pseudocholinesterase deficiency
Andermann syndrome	Glycogen storage disease type V	Pycnodysostosis
ARSACS	Hereditary thymine-uraciluria	Salla disease
Aspartylglycosaminuria	Niemann-Pick disease type C	X-linked juvenile retinoschisis
Ataxia with vitamin E deficiency		