

Cystic Fibrosis (CF)

Use

Quantitative determination of human immunoreactive trypsinogen (IRT) in blood specimens dried on filter paper is used as an aid in the screening of newborns for Cystic Fibrosis (CF).

Clinical Significance

CF is the most common recessive genetic disorder found in Caucasians with an incidence of about 1 in 3,200 live births in the US. One in 31 Americans is a carrier. The main clinical symptoms are characterized by functional abnormalities in the airway epithelium, the exocrine pancreas, the gastrointestinal tract, and the secretory duct of the sweat gland, leading to pancreatic and pulmonary insufficiency. Early detection of CF can decrease the risk of malnutrition, failure to thrive, zinc deficiency, fat-soluble vitamin (A, D, E, and K) deficiency-related disorders of the eye, bone, heart, and immune and nervous systems, and chest infections. Trypsinogen, one of the principal enzyme precursors produced by the pancreas, is abnormally increased in the blood of CF infants at birth due to obstructive pancreatic damage, making it a suitable marker for neonatal screening for CF. Heterozygous carriers of CF can also have elevated blood IRT values; therefore, it is not diagnostic in isolation. Generally, CF is characterized as “pancreatic insufficient” (PI) or “pancreatic sufficient” (PS), based on whether the individual has enough pancreatic function to grow and maintain health without supplemental pancreatic enzyme therapy (PERT). PI is the result of obstructive destruction of exocrine pancreatic tissue. About 85% of CF patients are PI before the age of 1 year. PI correlates closely with the specific *CFTR* mutations found in the individual. Over 2,500 mutations have been described, but most are very rare, with only five mutations reaching an allele frequency above 1%. $\Delta F508$ constitutes more than 85% of CF mutations. Individuals with 2 severe *CFTR* mutations (classes I, II, III, and VI) tend to have early PI, often beginning at birth, while those with 2 mild *CFTR* mutations (classes IV and V) or with one severe and one mild mutation tend to be PS at birth. However, there is considerable variation in genotype/phenotype correlates, indicating the critical role for environmental factors and modulatory genetic elements in clinical outcomes. CF individuals who are PS at birth may become PI at any age, and without symptoms initially, emphasizing the importance of constant monitoring.

Further information and ACT Sheets can be found at the OSDH Newborn Screening Program [website](#).

Methodology

GSP Neonatal IRT solid phase fluoroimmunoassay. Newborns with elevated IRT values or identified with meconium ileus or family history of CF are reflexed to 2nd tier *CFTR* gene mutation analysis using the xTag Cystic Fibrosis 39 kit v2 that identifies 39 mutations and 4 variants, including those currently recommended by the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG), plus some of the world’s most common and North American-prevalent mutations:

$\Delta F508^*$	1717-1G>A*	W1282X*	2307insA
$\Delta I507^*$	R560T*	1078delT	Y1092X
G542X*	R553X*	394delIT	M1101K
G85E*	G551D*	Y122X	S1255X [†]
R117H*	1898+1G>A*	R347H	3876delA
621+1G>T*	2184delA*	V520F	3905insT
711+1G>T*	2789+5G>A*	A559T	5T/7T/9T
N1303K*	3120+1G>A*	S549N	F508C
R334W*	R1162X*	S549R	I507V
R347P*	3659delC*	1898+5G>T	I506V
A455E*	3849+10kbC>T*	2183AA>G	

Specimen Type

See [Guidance for Collection of NBS Dried Blood Spots](#)

Minimum Volume/Size

See [Guidance for Collection of NBS Dried Blood Spots](#)

Collection Instructions

See [Guidance for Collection of NBS Dried Blood Spots](#)

Common Causes for Rejection

See [Guidance for Collection of NBS Dried Blood Spots](#)

Shipping

See [Guidance for Collection of NBS Dried Blood Spots](#)

Turn-around Time

IRT within 5 working days of receipt

IRT and *CFTR* mutation analysis within 7 working days of receipt

Reference Range

IRT < 57 ng/mL (Neonatal IRT); No mutations detected (*CFTR* mutation analysis)

Reportable Results

- Within Normal Limits
- Outside Normal Limits

Interpretation

- Within Normal Limits
 - Not consistent with Cystic Fibrosis, unless symptomatic, or if there is a family history of cystic fibrosis.
- Outside Normal Limits:
 - Elevated IRT and No *CFTR* Mutations Detected: Not consistent with Cystic Fibrosis, unless symptomatic, or if there is a family history of cystic fibrosis.
 - Elevated IRT and One *CFTR* Mutation Detected: Requires further testing; refer for sweat testing and genetic counseling. *CFTR* mutation analysis may be based on prior or current specimen. Mutation(s) detected - <<list mutation(s)/variant(s)>>
 - Elevated IRT and Two *CFTR* Mutations Detected: Consistent with Cystic Fibrosis; however, considerable clinical heterogeneity exists for individual *CFTR* genotypes; refer for sweat testing and genetic counseling. Mutation(s) detected - <<list mutation(s)/variant(s)>>

Limitations/Interferences

- The IRT assay is a screening test only. Other diseases may mimic PI CF, including other causes of PI, intestinal malabsorption, and some behavioral problems; a diagnostic procedure should be used to confirm a diagnosis of CF.
- False negative IRT values are known to occur in some CF newborns that present with meconium ileus. If an infant has meconium ileus or there is a family history of CF, it is important to mark the appropriate area of the NBS collection form, so that *CFTR* mutation analysis will be performed even if the IRT level is in the normal range.

- The Cystic Fibrosis 39 kit v2 assay can be used to confirm abnormal IRT values when two mutations are present in either homozygous or compound heterozygous states; however, because this kit only detects a subset of *CFTR* mutations, albeit common mutations for the US population, individuals with *CFTR* mutations may be missed. Testing of individuals with an expanded *CFTR* mutation panel that includes other less common mutations or *CFTR* sequencing may be indicated if the initial panel of mutations demonstrates a single mutation, or is suspected of having CF.
- A sweat chloride test should be an early step in the differential diagnosis of PI or malabsorption in newborns, and remains the “gold standard” for diagnosis of CF.
- Specimens improperly collected, processed or transported may result in erroneous results.

CPT Code

83516

Notes

The Neonatal IRT assay is approved for *in vitro* diagnostic use by the U.S. Food and Drug Administration. The xTag Cystic Fibrosis 39 kit v2 assay is a laboratory-developed test; performance characteristics have been validated and determined to be suitable for diagnostic purposes by the OSDH PHL. This test has not been cleared or approved by the U.S. Food and Drug Administration.