Newborn Screening and Confirmatory Testing for Cystic Fibrosis  
By Cynthia Kelley, MT (ASCP)

You may already be aware that the State of Kansas Newborn Screening program has recently started newborn screening for Cystic Fibrosis (CF). The State of Missouri has had a similar program in place since July 2005.

Cystic Fibrosis is the most common genetic disease in Caucasians, occurring in 1 of 2500 births. CF is an autosomal recessive genetic disorder characterized by chronic lung disease and nutritional deficiencies due to severe malabsorption. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene cause the body to produce thick, sticky secretions that obstruct passageways in the lungs and pancreas leading to lung infections and respiratory failure; blockage of pancreatic enzymes that lead to malnutrition; and infertility in affected males. The most common CF mutation is a three-base pair deletion called delta F508, but there are now over 1000 mutations identified in the CFTR gene.

The diagnosis of CF is made on the basis of one or more clinical symptoms or risk factors and laboratory evidence of cystic-fibrosis transmembrane regulator (CFTR) dysfunction. Clinical presentation and risk factors include: one or more phenotypic features; history of sibling with CF; or positive newborn screening. Laboratory evidence of CFTR dysfunction includes two abnormal sweat chloride determinations or presence of two disease-causing mutations in CFTR gene.

Newborn Screening

The identification of increased immunoreactive trypsinogen (IRT) levels in the blood of infants with CF has made neonatal screening for CF possible. Trypsinogen is one of the secretory products of the pancreas making its level in the blood a specific marker of pancreatic function. Detection of high levels of IRT in the newborn period places the infant at risk for CF. Although there is no cure, newborns screened for cystic fibrosis can benefit from early diagnosis and treatment, which can:

Improve growth
- Improve lung function
- Reduce hospital stays
- Add years to life

Immunoreactive Trypsinogen (IRT): Determination of (IRT) concentrations from dried blood spots serves as the basis for Missouri and Kansas Newborn Screening test for CF. IRT concentration is high in the blood of infants with CF, presumably from leakage of the protein into the circulation after exocrine pancreatic injury. Some infants that do not have CF may also have elevated levels of IRT in the newborn period, but these levels decrease to normal in the first weeks of life. Infants having persistently high IRT levels in the first weeks of life are considered at risk for CF. Therefore, an elevated IRT level in a newborn screen will require a repeat screen collected after 7 days and prior to 6 weeks of life to determine if a persistent elevation is present.
Timing Effect: Because IRT concentration is frequently high immediately after birth, specificity is improved if the test is performed after the first day of life. A specimen collected between 24 and 48 hours of life is optimal. If the IRT is elevated in the initial screen, a repeat screen should be collected after seven days of life and before six weeks of life to determine persistent elevations of IRT. Babies that are low birth-weight, premature and sick may require a third or fourth specimen to determine persistently elevated IRT levels. There is also an age-related decline in IRT levels in children with CF. IRT levels within the normal range will be considered non-interpretatable after 3 months of age and are not reported on the newborn screen.

Confirmation: All babies that demonstrate persistently elevated levels of IRT in the newborn screen should be referred for a Sweat Chloride Test (pilocarpine iontophoresis).

Sweat Chloride Testing
The Sweat Chloride Test, which determines the amount of chloride in the child’s sweat, has been the gold standard for diagnosis for 40 years and remains so today. Sweat chloride testing will detect roughly 99% of patients, is relatively inexpensive, and has a high degree of accuracy. Sweat Chloride Testing is performed by stimulating sweat production by pilocarpine iontophoresis. Sweat is collected on gauze pads or macroduct and analyzed for chloride content. The procedure is usually performed on the child’s arm but may be conducted on the thigh of small infants.

Sweat Chloride Test Interpretation:
- Negative: 0-40 mmol/L
- Borderline/indeterminate: 41-60 mmol/l
- Consistent with Cystic Fibrosis: >60 mmol/L

A Sweat Chloride Test of >60 mmol/L distinguishes most patients with Cystic Fibrosis; however normal Sweat Chloride concentrations are observed in approximately 1% of CF patients, generally with specific uncommon genotypes. Conversely it is important to recognize that there are clinical conditions that falsely elevate Sweat Chloride levels. Medical conditions most often associated with elevated Sweat Chloride levels other than Cystic Fibrosis include Addison’s disease, pulmonary edema, sepsis, pseudo-aldosteronism, hypoparathyroidism, and hypothyroidism. It is also very important to note that transient elevations can occur during the first 24 hours after birth. Therefore Sweat Chloride Testing should not be conducted on newborns less than 48 hours old.

Molecular Testing
There are a few special circumstances in which molecular genetic testing should be the initial diagnostic test:
- Testing infants who do not produce an adequate volume of sweat
- Testing symptomatic siblings of an affected individual in whom both CFTR mutations have been identified
- Prenatal testing
In addition, molecular testing is useful to aide in diagnosing patients with repeatedly borderline sweat chloride levels as well as providing prognostic information for patients clinically diagnosed with CF.

**CF Testing at CMHC**

- Sweat Chloride testing: The Cystic Fibrosis Foundation ([http://www.cff.org](http://www.cff.org)) sets the standards for the diagnosis and care of patients with Cystic Fibrosis. The Department of Pathology and Laboratory Medicine (DPLM) is accredited by the Cystic Fibrosis Foundation to conduct Sweat Chloride testing. The accreditation includes rigorous periodic inspections of the laboratory for its collection and testing procedures.
- DNA testing: The CMH Molecular Genetics laboratory now offers DNA testing for 25 of the most common CFTR mutations recommended by the American College of Medical Genetics for general screening. Please collect 1-3 ml in a lavender (EDTA tube) and allow one week for results.

**Scheduling an Appointment:** Sweat Chloride testing is available by appointment only due the length of time to complete (about 1 hour) and the complexity of the collection procedure. Only specially trained staff perform the collection procedure in order to reduce test failures and ensure the best possible care for patients.

**Locations and appointment availability:**

- Inpatients (M-F with same day schedule if required) 816.234.3230
- Outpatients Main Campus (three appointment times daily M-F) 816.234.3230
- Outpatients CM Northlands (one appointment time daily M-F) 816.413.2520
- Outpatients CM South (one-two appointment times daily M-F) 913.696.8210

To better serve our physicians and community the DPLM will begin centralized appointment scheduling through the Contact Center in early September. Information about this new service will be communicated via e-mail and physician mailings later this month.

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**CME Series**

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