

# NEWBORN SCREENING & CYSTIC FIBROSIS

## CYSTIC FIBROSIS ADDED TO THE NEWBORN SCREENING PANEL

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Cystic Fibrosis (CF) is the most common life-threatening genetic disorder in the United States, occurring in 1/3500 Caucasians; 1/11,000 Hispanics; 1/17,000 African Americans and much less in Asians.

Cystic fibrosis is caused when a defective protein disrupts the normal function of cells, which line the lungs, liver, pancreas, digestive and reproductive systems. CF leads to chronic lung disease, exocrine pancreatic insufficiency, hepatobiliary disease, and abnormally high sweat electrolytes.

CF has been described in literature since the early 17th century. CF was first scientifically named and described by Dorothy Anderson in 1938. In the 1950s, few children with cystic fibrosis lived to attend elementary school. The current life expectancy for



individuals is greater than 37 years old.

In the intervening 70+ years since Dr. Anderson's landmark paper, many advances in our understanding and treatment of this disease have occurred.

For example:

- Response to anti-microbial therapies have evolved.
- Pancreatic and fat-soluble vitamin supplements have been developed.
- More than 1500 mutations have been identified in the CFTR gene.
- Most mutations are associated with pancreatic insufficiency or severe CF.

- Mild mutations have also been identified that result in pancreatic sufficiency.
- Pulmonary disease progression or involvement cannot be completely predicted by mild or severe mutations.
- Pulmonary symptoms can be quite variable.
- Patients with severe mutations are usually diagnosed in infancy or childhood due to malnutrition and malabsorption concerns.
- Severe patients are more likely to present with meconium ileus or meconium peritonitis in the newborn period.

***Prevention of permanent lung injury, while providing nutritional support to ensure normal growth, has become the cornerstones of CF therapy.***

*Barbara Chatfield, MD is Professor of Pediatrics at the University of Utah and Director of the Intermountain Cystic Fibrosis Clinic located at PCMC Hospital.*

### Special points of interest:

The Newborn Screening Program Staff members are available for in-services, training and educational opportunities for your practice.

The Cystic Fibrosis Foundation (CFF) founded in 1955, is a non-profit organization dedicated to patients and families affected by cystic fibrosis.

The mission of the Cystic Fibrosis Foundation is to assure the development of the means to



[www.cff.org](http://www.cff.org)

cure and control cystic fibrosis and to improve the quality of life for those with the disease. CFF is dedicated to research, fund raising and advocating for families.

## GENETIC COUNSELING AND NEWBORN SCREENING *by Rena J. Vanzo, MS, Licensed Genetic Counselor*

Cystic fibrosis is a genetic condition that results from mutations within the cystic fibrosis transmembrane regulator (*CFTR*) gene. In order for a child to have symptoms of the condition, one *CFTR* mutation is inherited from each parent. This pattern is known as an autosomal recessive inheritance. The parents, who each harbor one *CFTR* mutation and are thus “carriers”, do not have symptoms of the condition. Because of this inheritance pattern, infants diagnosed with CF are oftentimes the first and/or only ones identified within their extended family. Without a thorough understanding of the

inheritance pattern, it is not surprising that families may be reluctant to accept their child could be affected with a genetic condition. This is especially true when the diagnosis is suspected in the newborn period before symptoms have begun. In addition to psychosocial considerations above, a diagnosis of CF may also raise questions regarding the genetic test results. Because of the potential for psychosocial concerns, the need for education regarding the inheritance of CF, and the possible confusion of genetic test results, it is important to offer families genetic counseling. This is a communication process which deals with the human problems associated

with the occurrence, or risk of occurrence, of a genetic condition in a family. Families will meet with a genetic counselor during the sweat chloride testing. A counselor, who has been trained in family dynamics, communication, and genetics, will provide a number of the family’s needs by through support and education outlined above, and can also assist in the acquisition of more comprehensive genetic testing, if necessary. Finally, a counselor will help the family recognize the impact of this infant’s diagnosis or carrier status on other family members. *This article was contributed by Rena J. Vanzo, MS, Licensed Genetic Counselor. For questions or comments contact her at: rena.vanzo@hsc.utah.edu.*

### ACMG DNA PANEL—31 MUTATIONS *By Norm Brown, BS MT Utah Public Health Laboratories*



In 1989, the gene responsible for CF was identified and named Cystic Fibrosis Transmembrane Conductance Regulator, or *CFTR*,

located on the long arm of chromosome 7; composed of 27 exons; spanning 250,000 bases. Seventy percent (70%) of the mutations are a three-base pair deletion resulting in the loss of a phenylalanine residue in position 508 ( $\Delta 508$ ).

Trypsinogen is a principle and sole secretory product of the pancreas and it’s

elevation has been identified as a marker for CF. The neonatal IRT, or Immunoreactive Trypsinogen assay is a solid phase, two-site fluorimetric assay based on the direct sandwich technique. Two monoclonal antibodies are directed against two separate antigenic determinants on the IRT molecule. The discovery that increased blood levels of IRT in infants with CF made large-scale screening possible in the newborn screening process.

*Norm is the Newborn Screening Section Chief at the Utah Public Health Laboratory*

**Testing will be done for the 31 known DNA mutations known to cause Cystic Fibrosis in the Utah Population.**  
 **$\Delta F508$  is found in 70-90% of cases – there are 1547 mutations identified to date.**

(<http://www.genet.sickkids.on.ca/cftr/app>)

#### Utah DNA Panel

1717-1G>A	A455E	R553X
1898+1G>A	$\Delta F508$	R560T
2184 $\Delta$ IA	G542X	W1282X
2789+5G>A	G85E	$\Delta 3876A$
3120+1G>A	N1303K	394 $\Delta$ ITT
3659 $\Delta$ C	R1162X	S549N
3849+10kbC>T	R117H	2055 $\Delta$ 9>A
621+1G>T	R334W	492F
R1066C	711+1G>T	R347P
E60X	406-1G>AS	
1507 $\Delta$	G551 $\Delta$	

- <1% of normal sweat test results in CF disease.
- 6-7% of borderline sweat tests result in CF disease.
- Borderline sweat tests are repeated and followed for one year.

### Sweat Testing: “THE GOLD STANDARD”

The sweat is collected and measured. In the sweat gland, defective chloride transport impairs sodium uptake in the sweat duct, resulting in elevated NaCl levels in sweat. Sweat testing is performed by stimulating sweat



**Infants < 2 months:**  
NORMAL <29  
BORDERLINE 30-59  
POSITIVE >60

production by pilocarpine iontophoresis. Sweat chloride has allowed effective non-invasive diagnosis and is considered the “gold standard” for CF testing. Primary Children’s Laboratory is the only Cystic Fibrosis Foundation approved laboratory in Utah.

## DOROTHY H. ANDERSEN 1901-1963

Dorothy Andersen, physician and pathologist discovered cystic fibrosis in 1935. That discovery came about while conducting an autopsy of a child who had died of suspected celiac disease, a nutritional disorder. During the autopsy, Andersen noticed a lesion in the pancreas. Following an extensive search of the autopsy records and related medical literature she discovered a clear, though previously unrecognized, disease



Dr. Andersen accepting the award for discovering Cystic Fibrosis

pattern. She named this disease cystic fibrosis.

Andersen and her research team made numerous discoveries and continued to work on diagnosing this new disease in living patients. This led to a simple diagnostic test for cystic fibrosis; one that is still in use today. (Ref: <http://www.faqs.org/health/bios/3/Dorothy-Andersen.html>)

In 1938, she published a landmark article on "Cystic Fibrosis of the Pancreas and its Relation to Celiac Disease" in the *American Journal of Diseases of Children*.

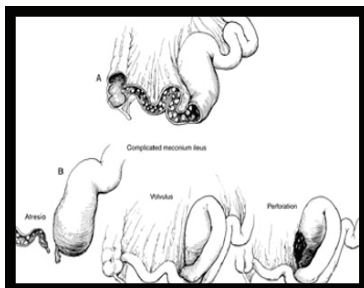
Dr. Andersen was routinely known as a "windblown" character who considered herself a rugged individualist; pediatric clinician; research chemist; as well as a roofer and carpenter. She is remembered to have an untidy lab, holding semi-annual Scandinavian "glüg" parties.

(Ref: [http://www.nlm.nih.gov/changingthefaceofmedicine/physicians/biography\\_8.html](http://www.nlm.nih.gov/changingthefaceofmedicine/physicians/biography_8.html)).

## MECONIUM ILEUS IN THE NEONATE PERIOD

**Meconium ileus (MI)** is most often seen in the first few days of life in neonates with cystic fibrosis, however IRT's remain at normal levels. Infants with a normal pancreas may also, yet rarely, present with a MI.

In cystic fibrosis, the abnormal pancreatic secretions, (deficiency of trypsin and digestive enzymes) leads to inspissated meconium that produces intestinal obstruction. The dilated coils of ileum contain the green, tarry or gritty meconium.



The colon beyond the ileocecal valve are not dilated, and little or no meconium is passed per rectum.

<http://library.med.utah.edu/WebPath/PEDHTML/PED046>.

<http://www.eapsa.org/parents/resources/meconium.cfm>

Graphics adapted from O'Neill: Principles of Pediatric Surgery. © 2003, Elsevier

### Intermountain Cystic Fibrosis Center

University of Utah and  
Primary Children's Medical Center

Appointments: 801-662-1765

Nurse's line: 801-662-1764

Fax: 801-662-1775

## CFTR: CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR PATHOPHYSIOLOGY

The pathophysiology of CF results from mutations in the cystic-fibrosis *transmembrane regulator (CFTR)* gene. The *CFTR* gene encodes a protein that regulates chloride transport.

This chloride transport, regulates multiple ion channels and cellular processes, especially the epithelial sodium (Na<sup>+</sup>) channel or ENaC activity.

In general, when mutations in *CFTR* result in a non-functional protein, the ENaC activity increases, and sodium transport across the membrane is augmented. In the lungs and intestine, this results in the accelerated uptake of



CFTR GENE

water from the lumen, leaving dehydrated mucous layers.

Conversely, in the sweat gland, defective chloride transport impairs sodium uptake in the sweat duct, resulting in elevated NaCl levels in sweat.

# PROPOSAL TO ADD CYSTIC FIBROSIS TO UTAH

In 2006, Dr. Jeff Botkin, MD PhD, chair of the Newborn Screening Subcommittee of the Genetic Advisory Committee, brought a proposal to add cystic fibrosis (CF) to the Utah Department of Health newborn screening of genetic disorders and diseases.

The initial task of the quarterly subcommittee meetings was to determine if CF met the requirements for screening under the guidelines developed by the Genetics Advisory Committee in the "Criteria for the Utah Newborn Screening Program". A review of the process to include cystic fibrosis began.

The collection and gathering of information from multiple experts, both in state and out of state was conducted. It was discovered that there are three different protocols followed by states.

- 1) SINGLE IRT [IRT]
- 2) IRT followed by recall IRT [IRT/IRT]

- 3) IRT followed by recall IRT, then DNA [IRT/IRT/DNA]

Based on the evidence, the IRT/IRT/DNA was approved as the most beneficial for Utah. Also, this protocol was concurrent with the Utah Statue 26-10-6 for mandated first and second specimens. The extensive review of each protocol unveiled that single IRT testing had large false positive rates. Infants often have an elevated IRT levels on first screens.

It was estimated that there would be 2500 abnormal levels on the first screen. As the infant grows, the IRT level decreases naturally. It was estimated 250 second specimens

will remain elevated.

In order to monitor the large amount of expected first abnormal IRT's, the

decision was made to report the first IRT as "indeterminate" and flag the specimen for IRT testing when the second newborn screening specimen was received. The medical home would not be contacted unless the second IRT remained elevated. Of the 250 second abnormal specimens, a sample of the blood spot would be submitted for DNA testing. The medical home would be notified that the DNA sample had been sent and to wait for the results. The expected number of identified infants that will be

carriers or have CF was approximately twenty-five infants. The infants identified with one or two alleles known to cause cystic fibrosis would be referred for confirmatory sweat testing.

An additional benefit of the IRT/IRT/DNA protocol would be to decrease the anxiety in the families who do not require confirmatory testing, as well as decrease the number of call outs to medical homes.

*Extensive research went into the decisions made.*

## THE GENETICS ADVISORY COMMITTEE

The Genetics Advisory Committee (GAC) was established to advise the Utah Department of Health (UDOH) on policy issues related to genetic services, including but not limited to newborn blood screening. The GAC is to provide guidance to programs and functions within UDOH having to do with genetic services and to ensure coordination of public health genetic programs in Utah with national efforts.

*Dr. David Viskochil is the current chairperson for the Genetic Advisory Committee.*

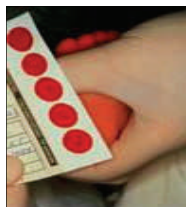


### SIGNATURE OF APPROVAL

Dr. David Sundwall, MD, Executive Director of the Utah Department of Health, reviewed and approved the GAC subcommittee proposal for testing to begin January 2009.

## NEWBORN SCREENING KITS

**FACT:** Everyday the Utah State Laboratory receives newborn screening specimen cards that are not filled out completely by the submitters.



The card is sent to the newborn screening staff to call the providers, parents and/or adoption agencies to gather the missing information.

### MISSING INFORMATION:

Missing information can take one day to one week to gather. This means an infant

may be at risk for a disorder that is not identified. Missing information means time consuming efforts for all parties that could have, and should have, been collected at the time of specimen collection.

**INSTRUCT:** Instruct all personnel to fill out the cards in their entirety.

**DID YOU KNOW?** If any information is missing, the blood spot specimen cannot be processed.

**DO IT RIGHT THE FIRST TIME!**

## NEWBORN SCREENING FOLLOW UP — WHAT CAN PROVIDERS EXPECT

The Utah Department of Health Newborn Screening Program (NSP) staff receives notice from the State Laboratory for every blood spot that has an abnormal or indeterminate result on all newborn screening specimens. The NSP follow up will notify providers using the following guidelines:



GUIDELINES FOR NOTIFYING PROVIDERS

Immunoreactive Trypsinogen (IRT), NSP will be notified and the infant's kit record will be marked to have a second IRT specimen run when the second newborn screening specimen is received at the State Laboratory.

indeterminate IRT and the result will be faxed to the submitter.

**Submitter:** Typically, the hospital or midwife submits the first newborn screening specimen; the pediatrician or medical home submits the second.

**Second Normal IRT:** When the second newborn screening specimen is received and the IRT is normal, that report will be faxed to the submitter and no follow up or notification will be provided.

**Routine Cystic Fibrosis:**

**(CF) results:** If the first newborn screening specimen has an elevated

**Reporting to Providers:** There will be a footnote on the newborn screening results acknowledging the

## OKAY— THE SECOND IRT IS ELEVATED—NOW WHAT?

**Second elevated IRT:** If the second specimen IRT remains elevated, a sample from the blood spot will automatically be sent for DNA testing. The panel for DNA testing will be for the 31 most common alleles known in the Utah CF population. Keep in mind there are over 1500 known alleles for CF.

**No Alleles:** When the DNA results are returned and there are no CF alleles identified for the Utah panel, NSP staff will notify the provider by telephone and a letter.

**One or two alleles:** In the instance one or more CF alleles are identified, the provider will be notified and a sweat test scheduled at Primary Children's Medical Center.

(PCMC is the only approved laboratory for sweat testing in Utah).

**Appointments:** Sweat testing is done by appointment only. The newborn screening staff will coordinate this appointment .

**Intermountain Cystic Fibrosis Center:**

Located at Primary Children's Medical Center; 100 N Mario Capecchi Dr., SLC, UT 84110; 801-662-1765.

**Barbara Chatfield, MD Director and Professor of Pediatrics, University of Utah**

## SWEAT TEST RESULTS ARE BACK—WHAT'S NEXT?

**Genetic Counseling:** While the sweat test is being performed a genetic counselor will be talking with the parents about Cystic Fibrosis, diagnosis, disease and genetics.

**SWEAT TESTING RESULTS**

**QNS:** Adequate sweat from infants is often difficult to

obtain and repeating the sweat test may be necessary. Parents know at the time of testing if repeating the test is required.

**Normal sweat test:** If the sweat test is normal (<29 mmol/L) no follow-up is necessary.

**Borderline:** Sweat tests that are borderline (30-59 mmol/L) will

require follow up for six months to one year at the Intermountain Cystic Fibrosis Foundation clinic.

**Positive:** CF is predicted when the sweat test is >60 mmol/L. Infants will receive an appointment within 1 week and treatment started.

Submitted by Karen Roylance, RN BSN  
Newborn Screening Nurse Consultant  
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## Utah Department of Health — Newborn Screening Program

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A simple blood spot can save a life



### Did You Know?

Cystic fibrosis is sometimes called "65 roses." The nickname came from a little boy who overheard his mom talking about the condition on the phone. He thought that each time his mom said "cystic fibrosis," she was talking about 65 roses.



65 Roses® is a registered trademark of the Cystic Fibrosis Foundation

## PRENATAL SCREENING

In 2001, The American College of Obstetricians and Gynecologists (ACOG) began recommendations that the **carrier screening test** be available to all pregnant women and their partners.

Approximately 1 in 30 Americans are a carrier of the CF gene. Family history and other factors are discussed concerning carrier screening testing, which is a blood or saliva sample.

Further information, prenatal pamphlets and brochures are available at: <http://www.acog.org>

