Cystic fibrosis (CF), or mucoviscidosis, is a genetically inherited multisystem disorder that affects the respiratory, gastrointestinal and reproductive systems. More than 1,800 different mutations have been discovered since the cystic fibrosis transmembrane conductance regulator (CFTR) gene responsible for CF was discovered in 1989 [1]. According to the CF Foundation’s National Patient Registry, the median age of survival for a person with CF is currently 33.4 years [2], with respiratory failure as the most common cause of death. Approximately 15% of individuals with CF have a mild form of the disease with a median survival of 56 years. Only thirty years ago, a CF patient was not expected to reach adulthood. Now, with the current diagnostic and treatment options, nearly 50% of CF patients live longer than 28 years [3].

The National Institute of Health (NIH), the American College of Medical Genetics (ACMG), and the American College of Obstetricians and Gynecologists (ACOG), along with other professional associations have released recommendations and developed guidelines for the application of genetic screening tests to clinical practice [4,5,6]. In 2011, ACOG updated its guidelines for prenatal and preconception carrier screening for CF. It has been recognized that while CF is more common among the non-Hispanic Caucasian and Ashkenazi Jewish population groups, the disease is becoming more prevalent in other ethnic groups and the population at large. Therefore, the updated guidelines recommend offering CF carrier screening to all women in pregnancy and for preconception evaluation [4,5,6,7,8].

### Epidemiology
- Approximately 30,000 people in the United States and 70,000 people worldwide have CF [2,3].
- Approximately 1,000 new CF cases are diagnosed each year [2].
- More than 10 million Americans are asymptomatic carriers of the defective CFTR gene [4].
- CF is the most common, life-threatening, autosomal-recessive condition in the non-Hispanic Caucasian population [2].
- CF is diagnosed equally in males and females [2].
- More than 75% of people with CF are diagnosed by age 2.
- Currently, ACOG recommends offering CF carrier screening to all women in pregnancy and for preconception evaluation. If a patient has been screened previously, CF screening results should be documented, but the test should not be repeated [5].
- NIH recommends screening as part of the newborn screening panels. The newborn screening panels that include CF screening do not replace maternal carrier screening [4].

### Pathogenesis
- CF is an autosomal recessive inherited disease: a person must inherit two copies of the defective gene, one from each parent in order to have CF. Carriers have only one copy of the defective gene and do not have symptoms of the disease. However, they can pass their mutation on to their children.
- In 1989, the CFTR gene associated with CF was identified and mapped to the long arm of chromosome 7.
- More than 1,800 known mutations of the CFTR gene have been discovered.
- The first mutation identified was ΔF508. This major mutation has been determined to account for almost 70% of the CF cases in the United States.
- The W1282X mutation occurs more frequently in the Ashkenazi Jewish population compared with other ethnicities [2,3,5].

### Clinical Significance
- CF is a multisystem disease with morbidity and mortality resulting from chronic obstructive pulmonary disease and respiratory failure being the primary cause of death among > 90% of CF patients.
- CF does not affect intelligence or mental capacity and there are no physical features attributed to the disease.
- Symptoms may include very salty tasting skin, persistent coughing, frequent lung infections, wheezing or shortness of breath, excessive appetite but poor growth/weight gain, and greasy, bulky stools.
- More than 95% of males with CF have primary infertility with obstructive azoospermia due to congenital bilateral absence of the vas deferens.

### Table 1: Incidence Rate and Carrier Risk for Cystic Fibrosis based on ethnicity [2,4].

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Carrier Risk</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian American</td>
<td>1/29</td>
<td>1/ 3,200</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>1/24</td>
<td>1/3,000</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>1/46</td>
<td>1/ 8,000 – 9,000</td>
</tr>
<tr>
<td>African American</td>
<td>1/65</td>
<td>1/ 15,000 - 17,000</td>
</tr>
<tr>
<td>Asian American</td>
<td>1/94</td>
<td>1/ 31,000 - 100,000</td>
</tr>
<tr>
<td>Overall US population</td>
<td>1/31</td>
<td>1/ 3,500</td>
</tr>
</tbody>
</table>
The major 23 mutations recommended by ACOG and ACMG are indicated in bold font.

* The 9 mutations recommended by the FDA for determining Ivacaftor treatment efficiency are indicated in italics.

**Laboratory Diagnosis**

- The sweat test (pilocarpine iontophoresis), is a standard diagnostic test for CF. Sweat chloride levels > 60mEq/L are considered diagnostic for CF [7,8].
- Molecular approaches for the detection of CFTR mutations include two main options: 1) targeted mutation analysis or 2) sequencing of the CFTR gene.
- Initially, the American College of Medical Genetics Cystic Fibrosis Carrier Screening Working Group recommended that laboratories use a pan-ethnic panel of 25 mutations that were present in at least 0.1% of patients with classic CF. The current ACOG and ACMG guidelines approved December 16, 2010 use a 23-mutation panel for CF screening [5,6].
- Complete analysis of the CFTR gene by DNA sequencing is valuable for patients with CF, patients with a family history of CF, males with congenital bilateral absence of the vas deferens, or newborns with positive newborn screening, but negative by targeted analysis.
- Genetic counseling is important to discern whether the combination of mutations and variants would cause classic or atypical CF.
- The MDL Cystic Fibrosis Core Test is a CFTR gene sequence analysis screen, utilizing Next Generation DNA sequencing technology, for the 23 major mutations approved by ACOG and ACMG for CF screening [5,6,9].
- The MDL Cystic Fibrosis Comprehensive Test is an expanded CFTR gene sequence analysis screen, utilizing Next Generation DNA sequencing technology, for 191 variants, including the set of 23 major mutations approved by ACOG and ACMG for CF screening and 9 mutations recommended by the FDA for determining Ivacaftor treatment efficacy [5,6,10].
- The MDL Cystic Fibrosis Site Specific Analysis screens for known family CF mutations previously identified in blood relatives.

**Table 2: MDL Cystic Fibrosis Core Panel**

<table>
<thead>
<tr>
<th>ΔF508</th>
<th>R553X</th>
<th>R1162X</th>
<th>2184delA</th>
<th>ΔI507</th>
</tr>
</thead>
<tbody>
<tr>
<td>621+1G&gt;T</td>
<td>G85E</td>
<td>3849+10kbC&gt;T</td>
<td>G542X</td>
<td>R117H</td>
</tr>
<tr>
<td>R334W</td>
<td>2789+5G&gt;A</td>
<td>G551D</td>
<td>1717+1G&gt;A</td>
<td>R347P</td>
</tr>
<tr>
<td>3659delC</td>
<td>W1282X</td>
<td>A455E</td>
<td>711+1G&gt;T</td>
<td>3120+1G&gt;A</td>
</tr>
<tr>
<td>N1353K</td>
<td>R560T</td>
<td>1898+1G&gt;A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: MDL Cystic Fibrosis Comprehensive Panel**

<table>
<thead>
<tr>
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- The major 23 mutations recommended by ACOG and ACMG are indicated in bold font.
- The 9 mutations recommended by the FDA for determining Ivacaftor treatment efficiency are indicated in italics.

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Benefits of Non-Invasive Testing

- MDL provides non-invasive, easy specimen collection methods for CF testing using either mouthwash samples or cervico-vaginal swabs. Blood is also an acceptable source.
- Utilizing innovative Next Generation DNA Sequencing technologies, MDL provides an extremely high accuracy of genetic testing.
- Specimens collected using the MDL non-invasive kits yields sufficient material for the DNA sequencing technology.
- MDL Cystic Fibrosis tests are designed in full compliance with all official guidelines for cystic fibrosis screening and diagnosis [5,6,7,8].

Diagnostic Considerations

- The ACOG Committee Opinion 486, released in April 2011, recommends preconception CF carrier screening for all women of reproductive age. “It is becoming increasingly difficult to assign a single ethnicity to individuals. It is reasonable, therefore, to offer CF carrier screening to all patients” [5].
- If a patient has been screened previously, CF screening results should be documented, but the test should not be repeated.
- Newborn screening panels that include CF screening do not replace maternal carrier screening. Newborn screening for CF can be performed as early as 2 days after birth.
- For couples in which both partners are carriers, genetic counseling is recommended to review prenatal testing and reproductive options.

Treatment Options

- As with many other genetic disorders, CF has been considered a disease with no available cure.
- While there is no cure for CF, patients must follow a regular treatment routine to maintain optimal lung function, prevent infections and support pancreatic function.
- Pharmaceutical companies continue to research in order to develop treatment options for CF.
- Ivacaftor (Kalydeco™) was approved by the FDA in 2012 for the treatment of CF patients with the G551D mutation in the CFTR gene. On February 21, 2014, the FDA approved the expanded use of Kalydeco™ for additional mutations underlying CF: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R [10].

Frequently Asked Questions

Q: Can cystic fibrosis testing be performed without blood?
A: Absolutely. Since this is a genetic test, the mouthwash sample or cervico-vaginal swab contains a very high DNA yield from the epithelial cells that can be analyzed using a DNA sequencing platform. However, if a blood sample is submitted, the screening for CF mutations can be performed as well. For any cervico-vaginal swab samples that tests positive for a mutation, MDL will automatically perform an assay for male DNA to rule out the possibility of any sampling contamination from recent sexual intercourse.

Q: How many mutations does the MDL CF Test detect?
A: The MDL CF Core Panel detects the major 23 mutations (including ∆F508) that have been determined to account for the majority of cases in the United States. The MDL CF Comprehensive Panel screens for 191 variants, including a set of 23 mutations approved by ACOG and ACMG guidelines for CF screening and 9 mutations recommended by the FDA for determining Ivacaftor (Kalydeco™) treatment efficacy. The MDL CF Site Specific Analysis is performed specifically for known family CFTR gene mutations.

Q: What should I do if a patient tests positive for CF?
A: A “positive” carrier test for CF means that a person has one mutation of the CF gene. This result is more than 99% accurate. Carriers of single CF mutations are generally asymptomatic and experience no discernible health problems. ACOG guidelines recommend offering CF screening to both parents before/during pregnancy, because in order to pass on the disease CF disease, a child must inherit one copy of a mutation of the CF gene from each parent.

Q: What should I do if a patient tests negative for CF?
A: With more than 1,800 different mutations of the CF gene, there are some rare disease-causing mutations that the test may not find. If your test is negative for a mutation of the CFTR gene, there is still a small chance you could be a carrier of one mutation. The chance depends on your race or ethnic group and the number of mutations the test was validated to detect.

Q: Do I need to test the patient every pregnancy?
A: No. Every patient should be asked if she has been already tested. According to ACOG guidelines, the test should not be repeated if the patient has been screened before. The result of the previous test should be noted in the patient’s medical record for each subsequent pregnancy.

Q: Should I screen the patient if her newborn CF screening results are available?
A: Yes. According to ACOG/ACMG guidelines, newborn screening panels that include CF screening do not replace maternal carrier screening.

Q: Traditionally, I have only tested certain ethnic groups for CF. Should I reconsider this policy?
A: ACOG guidelines recommend offering CF carrier screening to all patients of reproductive age due to the difficulty of assigning a single ethnicity to individuals.
References

1. Cystic Fibrosis Mutation Database. Available at: http://www.genet-sickkids.on.ca/Home.html.


