



CCMG Position Statement:

Newborn Screening for Cystic Fibrosis

Approved by the CCMG Board of Directors July 13, 2010

Purpose

The aim of this statement is to provide recommendations regarding newborn screening for Cystic Fibrosis (CF) in Canada.

Methods of Statement Development

Members of the Canadian College of Medical Geneticists (CCMG) Clinical Practice committee reviewed the relevant literature on newborn screening for CF. Recommendations were developed for health care providers in Canada. The recommendations were circulated for comment to the CCMG members-at-large and, following appropriate modification, approved by the CCMG board of directors.

Introduction and Literature Review

Multiple reviews have been published on the topic of newborn screening for CF^(1,2,3,4,5,6,7). Most argue in favor of screening. The Cochrane Collaboration reviewed two studies that met their inclusion criteria i.e. randomized control trials on newborn screening for CF that looked at specific outcomes including objective measures of lung function, chest radiograph score, nutritional status and survival⁽¹⁾. The two included studies were the UK trial and the Wisconsin trial. Multiple reports from those trials were reviewed and data were available on 1,124,483 screened newborns with 210 cases of CF followed for a maximum of 17 years. They concluded that identification of infants by CF screening benefits their growth and prevents malnutrition which can adversely affect cognitive function. They also concluded that pulmonary benefits are likely in early childhood. Confounding factors biased the data on long term pulmonary function. The expense of CF screening is less than when the disease is diagnosed clinically. For example, according to one analysis with screening by IRT and DNA, the cost per newly diagnosed cases by screening was US \$9,025 and by diagnosis based on traditional methods was US \$16,846. Based on a workshop held in 2003, the Center for Disease Control believes that newborn screening for CF is justified⁽⁵⁾. The American CF Foundation currently recommends that all states should routinely screen for CF in newborns⁽⁸⁾. Possible concerns which are not supportive of newborn screening for CF include the potential for delayed diagnosis after a false-negative screening test and difficulties disproving CF in a baby with one identified mutation (2).

The literature provides evidence of wide support for newborn screening for CF among parents of affected infants and among carrier families⁽⁹⁾. Dhondt provided evidence that newborn screening for CF is acceptable to the population in general based on a low refusal rate (0.2% after the first year of screening) in the French screening programme (10).

Multiple approaches to screening are possible^(5,11). Measurement of Immunoreactive Trypsinogen (IRT) on a newborn blood spot is the first line test. Second tier tests include various combinations of repeat IRT measurements, sweat chloride determination and molecular testing for CFTR mutations. Each method will vary in cost and screening performance. The sensitivity of various protocols has been reported to range from 86% to 99%. The Wisconsin trial reported a 99% sensitivity with a 99% specificity, using a protocol where analysis for 25 CFTR mutations was done on a sample if the IRT was > 94th %ile⁽¹²⁾.

In 1968, Wilson and Jungner published their classic criteria for conditions suitable for screening (13). Eight of the criteria are specific to the disease and based on the information discussed above, newborn screening for CF does meet these criteria. Two of the screening criteria are programme issues rather than disease specific, i.e. there should be an agreed policy on whom to treat as patients and case-finding should be a continuing process. Each screening programme would be responsible for ensuring that these last two criteria are met

According to the CF Foundation website, all 50 states and the District of Columbia will require newborns to be screened for CF by 2010⁽⁸⁾. According to the Canadian CF Foundation website as of August 2010, British Columbia, Alberta, Ontario and Saskatchewan offer newborn screening for CF⁽¹⁴⁾. The protocols are listed in the table. Some programmes may deal with some unique populations which require consideration when protocols are being developed. For example, the M1101K mutation accounts for about two-thirds of CF mutations seen in the Hutterite population and would not be detected by the 41 mutation panel routinely used for CF testing for the Manitoba population⁽¹⁶⁾. It should be noted that the prevalence of CF is lower in non-European populations, and thus, the efficacy of population based screening could be lower in populations where there is a lower proportion of Europeans than in the published literature. As well, the detection rate of causative mutations in non-European populations is lower, and variable. If a newborn from a non northern European population has a screen positive IRT, molecular diagnosis might be less effective. Educational materials should incorporate this information. Newborn screening for CF also has the potential to identify infants with mild or atypical CF⁽¹⁷⁾. The educational material provided should therefore also discuss this possibility.

CF screening programmes that utilize molecular testing also will detect CF carriers. Genetic counselling should be available for families of carriers including the offer of cascade carrier testing of relatives. This is especially true in Canada where routine carrier screening for all women during pregnancy is not recommended (18).

Province	British Columbia ⁽¹⁵⁾	Alberta ⁽¹⁶⁾	Saskatchewan ⁽¹⁷⁾	Ontario ⁽¹⁸⁾
IRT cut-off for molecular testing	>97 %ile	> 60ug/L or 98 %ile	>150 ng/ml on 1 st sample or >60 ng/ML on 2 nd sample	>96 %ile
CF molecular Panel	Inplex CF Invader Assay (Hologic, Inc); 39 mutation kit which include the ACMG panel) ^{19,20}	Tm Biosciences Tag-It CFTR 39+3 mutation kit.	Tm Biosciences Tag-It CFTR 39+3 mutation kit.	Tm Biosciences Tag-It CFTR 39+3 mutation kit.
Indications for counselling/ follow-up/sweat test	1 or 2 mutations identified or IRT >99.9 %ile	1 or 2 mutations identified or IRT >99.9 %ile	>150 ng/ml on 1 st sample or >60 ng/ML on 2 nd sample and mutation found	1 or 2 mutations identified or IRT >99.9 %ile
Further details	If high IRT and 1 CFTR mutation, 2 nd blood spot on day 21. If IRT is elevated sweat test recommended. If IRT normal, family given option of sweat test or follow-up by primary care provider		2 nd blood spot if collection <7 days and IRT between 80 & 150 ng/ml or if collection not < 7 days and IRT between 60 and 150 ng/ml.	

One potential concern relating to newborn screening for CF is the issue of inconclusive results. CF can be considered confirmed if two disease causing CF mutations are identified. In addition, with rare exceptions, a diagnosis of CF can be made if the sweat chloride is > 60 mmol/L and can be excluded if the sweat chloride is < 30mmol/L⁽⁶⁾. Therefore, the diagnosis remains uncertain if one or no mutation is found and the sweat chloride level is between 30 and 60 mmol/L. In this situation, full gene sequencing may be required to determine the status of the patient.

Recommendations

- 1) All provincial newborn screening programmes should offer screening for cystic fibrosis. This should include adequate resources for diagnosis, counselling and testing of affected persons, as well as relatives at risk of being a carrier.
- 2) Each programme should decide on the specifics of the screening protocol used. In general, IRT would be the first line test with molecular tests used as a second or third line test.
- 3) Each programme should adjust their screening protocols including educational materials to fit their local population.
- 4) Educational materials should discuss the potential diagnosis of mild or atypical CF.
- 5) Each newborn screening programme should monitor and review the screening results from a quality control perspective.

- 6) Infants with confirmed or suspected cystic fibrosis should be referred to CF clinics for management.
- 7) Families of affected or carrier infants should be offered a referral for genetic counselling and potential cascade carrier screening.
- 8) Full CF gene sequencing should be available when required to clarify inconclusive results.

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