UK National Screening Committee

Antenatal screening for cystic fibrosis

28 June 2019

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not antenatal screening for cystic fibrosis (CF) meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. Antenatal screening for CF is not currently recommended in the UK.

3. This recommendation was last considered by the UK NSC in July 2006, the same time at which implementation of the current newborn screening programme was being considered. A review of antenatal screening was not undertaken at this point because the emphasis was on the newborn programme.

4. Carrier testing is available for blood relatives of people with a diagnosis of CF and their partners (cascade screening). Couples who are carriers may be offered testing (such as chorionic villus biopsy or amniocentesis) during pregnancy, to identify if the baby has the condition. A small proportion of CF carrier babies are also detected incidentally through the newborn screening programme. However, population-based or universal antenatal carrier screening is not currently performed in the UK.

5. The population screening recommendations were primarily informed by a 1999 Health Technology Appraisal (HTA) which reviewed antenatal screening alongside alternative screening options, (preconception, population, newborn and cascade screening).

Evidence Summary

6. The 2019 review was undertaken by Bazian in accordance to the UK NSC evidence review process https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process.

7. The review aims to evaluate is whether the evidence is available to support population-based antenatal screening for CF. Such a programme would either screen both parents at the same time (couple screening) or sequentially, where the second parent was screened

only if the first parent was found to be a CF carrier (stepwise or sequential screening). If both parents were carriers, the couple could be offered antenatal testing (amniocentesis or chorionic villus sampling) to see if the baby carried 2 disease-causing CF variants. The purpose would be to support informed pregnancy decision making.

8. The focus of the review was based on issues identified in the 1999 HTA and on intermittent discussion within the FMCH since 2012 on the basis of rapid review documents. The main conclusion of the discussion was that greater clarity was required about the genotype-phenotype correlation and the clinical course associated with the different combinations of mutations. This has major implications for screening policy and was considered a pre-requisite for further discussion of antenatal screening.

9. The following key questions were addresseed:

    I. What is the UK prevalence of CF and CF carrier status among the general population, by genotype and by ethnicity? Has prevalence changed over time? (Criterion 1)

    II. What are the genotype-phenotype associations in cystic fibrosis patients, including their clinical prognosis? (Criterion 1)

    III. What genotypes/variants are covered by commercially available antenatal CF screening tests in the UK? What is the clinical sensitivity of these tests for predicting CF in the fetus/newborn? (Criteria 4 and 8)

    IV. Is an antenatal screening programme acceptable to people in the UK, specifically to pregnant women and their partners, to people with CF carrier status, and people affected by CF (patients or family members)? (Criterion 12)

10. Based on the synthesis of evidence against the UK NSC criteria this review concluded that population-wide antenatal screening programme for CF should not be introduce in the UK at the current time. This recommendation is made for the following reasons:

    I. There were up-to-date data on the prevalence and incidence of the condition in the UK currently and over the time; although, there was no data on prevalence or incidence by ethnicity or on CF carrier prevalence. **This part of criterion 1 was met**. Overall, there is evidence of an association between genotype and phenotype. However, due to the variability in outcomes for individuals, risk of bias across studies (particularly relating to lack of genotyping and confounding), limited

applicability to care today, and uncertain effects of rare variants, there is insufficient evidence to reliably predict the genotype-phenotype association. **This part of criterion 1 was not met.**

II. No studies have been published investigating antenatal screening in the UK since 2000. Only a single screening pilot Australia study was found looking at the practical experience of antenatal CF screening performed over the past 18 years. There was no follow-up of screen-negatives so further test accuracy data was not available. This study also had limited applicability to the UK as it was a pay-for service, included preconception screening and tested for variants prevalent in the local population (not all of which are common in the UK). Because of the low volume of evidence, limited applicability and risk of bias, these criteria are not met**. Criteria 4 and 8 were not met.**

III. Some studies exploring views on universal antenatal CF screening in non-UK settings were identified by the search. However no studies have assessed views on universal antenatal CF screening among the UK population. Based on an absence of UK evidence this criterion is not met. **Criterion 12 was not met**

Consultation

11. A three-month consultation ending on the Monday 20th May 2019 was hosted on the UK NSC website. Direct emails were sent to 13 stakeholder organisations. **Annex A**

    Only one set of comments was received following the public consultation from the Royal College of Midwives which supported the conclusions of the evidence summary. (See **Annex B** for comments)

Recommendation

12. The Committee is asked to approve the following recommendation:
    An antenatal population screening programme for cystic fibrosis is not recommended in the UK.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Condition	
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	**Prevalence and incidence – met** **Genotype-phenotype association – not met**
The test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
8. If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.	**Not Met**
The screening programme	
12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	**Not Met**

UK National Screening Committee

Annex A

List of organisations contacted:

1. Cystic Fibrosis Trust
2. Faculty of Public Health
3. Genetic Alliance UK
4. Institute of Child Health
5. PHE ANNB Screening Programmes
6. PHG Foundation
7. Royal College of General Practitioners
8. Royal College of Midwives
9. Royal College of Obstetricians and Gynaecologists
10. Royal College of Physicians
11. Royal College of Physicians and Surgeons of Glasgow
12. Royal College of Physicians of Edinburgh
13. Wolfson Institute of Preventive Medicine

UK National Screening Committee

Annex A — Consultation comments

Name:	Mervi Jokinen	**Email address:**	xxxx xxxx
Organisation (if appropriate):	The Royal College of Midwives		
Role:	**Professional Advisor**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes x☐ No ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 10; recommendation on screening	**Recommendations on screening** The findings indicate that the current policy not to perform population-wide antenatal screening for CF should not be reversed at the current time.	RCM agrees with the recommendation that antenatal screening for CF is not performed at the current time based on the answers presented to the review questions.
Page 6; Current CF screening programmes in UK	Since 2007 screening for CF in the UK has been carried out as part of the newborn blood spot (NBS) screening programme. The purpose of newborn screening is to allow for early diagnosis and treatment. There is no curative treatment for CF but life expectancy continues to improve.	As the findings show, the bloodspot screening programme has impacted in earlier diagnosis and treatment; combined with new treatments, there is a gradual positive increase in life expectancy. RCM believes in future the further developments in the pharmagenomics may be a more effective target to address, removing some of the uncertainties in developing an antenatal screening programme.
Executive Summary p. 10	Pre-2000 UK pilots had also differed in the variants they tested for and the background literature indicates that there is as yet no well-established variant panel that could be used in an antenatal	In view of the absence of agreed panel of variants, RCM agrees the screening would not be effective as a universal screening programme. .

	screening test for CF in the UK. **Criteria 4 and 8 – not met.**	
Executive summary: Evidence uncertainties p. 11	3. To establish a panel of variants that could be used in antenatal screening in the UK and to conduct further antenatal screening pilots in the UK that use these variants. Such studies would benefit from conducting longer term follow-up and surveillance of all screen-negatives to give an indication of clinical sensitivity, specificity, positive and negative predictive values of the test.	RCM agrees with the recommendation for future studies to establish a panel of variants, that could be used in antenatal screening in the UK and to conduct further antenatal screening pilots in the UK that use these variants. This may or may not be linked to better informed decision making by the parents regarding the pregnancy and hopefully can advance the treatment options via future pharmacogenomics.