Early assessment of an emerging test for non-invasive prenatal diagnosis

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Karla Douw
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Early assessment of an emerging test for non-invasive prenatal diagnosis

Preamble

This early assessment was commissioned by biotechnology company, FCMB (Foetal Cells in Maternal Blood), in June 2006. The aim was to provide an assessment, based on current knowledge, of the likely consequences of introduction in Danish health care of an emerging blood test to detect foetal abnormalities.

The assessment was undertaken during August-October 2006. Earlier drafts of this assessment have been discussed with Prof. Steen Kølvraa, FCMB, Søren Brahe Bohnsen, project manager at INCUBA, and Claire Gudex, consultant at the Centre for Applied Health Services Research and Technology Assessment, University of Southern Denmark.

Informal discussions about the technology and possible consequences of its application in Danish health care have been held with Prof. Niels Uldbjerg, Department of Obstetrics and Gynaecology, Skejby University Hospital, and consultant Kirsten Rasmussen, Department of Clinical Genetics, Odense University Hospital.
1. Introduction

An early assessment aims to assess the potential clinical, organizational, economic, social, legal and ethical consequences of an emerging or new health technology to the health care market in the 0 to 5 years before its introduction.

A new non-invasive prenatal blood test based on foetal cells circulating in maternal blood is being developed by biotechnology company FCMB (Foetal Cells in Maternal Blood). FCMB is a biotechnology company that was established in 2005 and has locations at Vejle Hospital and Århus University Hospital. FCMB’s current activities focus on generating a monoclonal antibody to detect the foetal cells.

This early warning has been prepared using written information provided by the company (FCMB, 2006), relevant literature on prenatal screening and diagnostics, and consultation with two clinical experts - a clinical geneticist and a specialist in obstetrics and gynaecology.

2. The emerging FCMB test

The FCMB blood test can be used to diagnose chromosome disorders. More specifically, the new test will diagnose numerical chromosomal abnormalities of five chromosomes, namely #13, #18, #21, X and Y chromosome, i.e. those that are the focus of current Danish screening practices using the double test and assessment of nuchal translucency. The FCMB test is thus designed to find the same chromosomal abnormalities as the current screening tests. The difference is that the new test would diagnose the presence of abnormalities (i.e. provide certainty about) rather than provide a risk assessment as the current screening tests do.

Since foetal cells are present in the maternal circulation throughout most of the pregnancy, the test can replace both chorionic villus sampling (CVS), which is best performed around gestational weeks 10-11, and amniocentesis (AC), which is best performed at gestational weeks 15-17 (National Board of Health, 2003). As the FCMB test is non-invasive, it does not have an associated risk of miscarriage (as is the case with both CVS and AC), and it can be repeated without extra risk.

At present, the FCMB test is not designed to provide the full spectrum of diagnostic information that can be obtained from CVS and AC, both of which involve full karyotyping of the foetal DNA. The new test cannot be used, therefore, to test for either mosaicism1 or structural chromosomal defects. Furthermore, as the FCMB test looks only at chromosomes, it is not suitable for identifying monogenic disorders, such as cystic fibrosis (personal communication, Steen Kølvraa, FCMB, August 2006).

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1 Mosaicism refers here to the situation when abnormal cells are only confined to the placenta and not to the foetus
3. Current non-invasive prenatal screening in Denmark

**Routine screening**
A new Danish policy on prenatal diagnosis and screening was issued in September 2004. The screening programme includes the offer to all pregnant women of a first trimester serum test and an ultrasound scan for nuchal translucency assessment (Eurocat, 2005). Furthermore, all women are offered a routine ultrasound scan for structural anomalies at about week 18.

**First trimester serum test (double test)**
The first trimester serum test is also called the double test as it tests for two substances in the mother’s serum: pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotrophin (beta HCG). The test is done at gestational age 8+0 to 13+0, and the results are available within 2 days. The results of the analysis are compared to normal standards for the gestational age and are used, together with the risk associated with the mother’s age, to calculate the risk of the child having trisomy 21, 18 or 13 (Down’s syndrome, Edwards syndrome or Patau’s syndrome). When the double test is used in isolation it can detect 70-75% of all pregnancies with Down’s syndrome, and 5-8% of the pregnant women will be offered invasive prenatal genetic diagnostics (SSI, 2006).

**Nuchal translucency**
Nuchal translucency assessment (NT) involves the use of ultrasound to measure the collection of fluid under the skin at the back of the foetus’ neck. NT is carried out at gestational age 11+0 to 13+6. Nuchal thickness is a marker for associated chromosome abnormality, particularly Down’s syndrome and Turner’s syndrome, as well as heart and skeletal problems (see figure 1). The ultrasound data are used to calculate the child’s risk of having a chromosome abnormality. The combination of the double test and NT has a higher detection rate than the double test alone, with the result that fewer women are offered invasive prenatal diagnostics (National Board of Health, 2003).
Figure 1 Ultrasound image of a foetus. The thickness of the edema in the neck region is measured between the two marks (Source: FCMB)

**Triple test**

The triple test is not part of routine prenatal screening in Denmark, but may be undertaken if, for example, the double test has not been carried out. The triple test is done in the second trimester and preferably at 15-18 weeks. A sample of blood is taken from the mother to measure the levels of three biochemical markers: human chorionic gonadotrophin (hCG) and estriol, both of which are produced by the placenta, and alpha-fetoprotein (AFP), which is produced by the foetus. Maternal blood levels can identify a foetus at risk for neural tube defects (e.g. spina bifida) or chromosomal abnormalities (e.g. Down’s syndrome). Just as with the double test, the risk assessment takes the mother’s age into account (SSI, 2006).

4. **Current practice of invasive prenatal diagnostics**

Abnormal test results on the double test, NT or triple test indicate a need for further evaluation of the foetus. Risk thresholds for invasive prenatal diagnostics are:
- double test + NT risk 1:250 or higher
- double test + triple test risk 1:250 or higher
- double test + NT + triple test (integrated test) risk 1:250 or higher.

Other indications for invasive prenatal diagnostics include a family history of chromosome anomaly, and malformations diagnosed by ultrasound (Eurocat, 2005).
Invasive diagnostics include chorionic villus sampling (CVS) and amniocentesis (AC). CVS is best performed in the first trimester, between 9-13 weeks, and AC between 14-18 weeks (National Board of Health, 2004).

With the current screening programme in Denmark it is expected that CVS will be the more common invasive technique in the event of a high risk foetus on the basis of the double test and NT, as AC will not be carried out before 15 weeks (Tabor and Uldbjerg, 2005).

CVS and AC
CVS involves the removal of a sample of placental tissue from the uterus (see figure 2). This is done either by the insertion of a needle, guided by ultrasound, through the abdomen and into the uterus, or by threading a catheter into the vagina and through the cervix. AC involves the withdrawal of a sample of amniotic fluid from the uterine cavity using an ultrasound-guided needle that is inserted through the abdomen (see figure 3).

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[Image 2: Principle of chorion villus sampling (Source: FCMB)]

Figure 2 Principle of chorion villus sampling (Source: FCMB)
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The tissue from both tests is examined for evidence of numerical and structural chromosome abnormalities, metabolic diseases and monogenetically inherited diseases, such as cystic fibrosis.

The advantage of CVS is that it can be carried out 9-13 weeks after the last menstrual period, i.e. earlier than AC, which is carried out at 14-18 weeks. When a full cytogenetic analysis (full karyotype assessment) is conducted, CVS has a further advantage over AC in that the results are available within 1-2 weeks, whereas AC results take 2-3 weeks. Both diagnostic tests have a risk of between 0.3%-1.5% of causing a miscarriage (DSOG, 2001).

In recent years other techniques have been developed that can provide a faster diagnosis of chromosomal abnormalities. These PCR-based techniques and the FISH technique involve the use of uncultured cells obtained through CVS and AC and can therefore provide results within 2 days. Both tests detect only certain chromosome abnormalities, however, and are used only in cases where a rapid answer is needed (Lundsteen & Schwartz, 2003). Despite their limitations, the tests are a reliable way of testing for defined abnormalities with a high diagnostic accuracy (National Board of Health).

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2 Polymerase chain reaction (PCR) is a technique which is used to amplify the number of copies of a specific region of DNA, in order to produce enough DNA to be adequately tested. This technique can be used to identify with a very high-probability, disease-causing viruses and/or bacteria, a deceased person, or a criminal suspect.

3 Fluorescent in situ hybridization (FISH) is a cytogenetic technique which can be used to detect and localize the presence or absence of specific DNA sequences on chromosomes. It uses fluorescent short pieces of DNA which bind only to those parts of the chromosome with which they show a high degree of sequence similarity.
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2003). The sensitivity for trisomy\(^4\) and triploidy\(^5\) is 100% without any false-positive cases (National Board of Health, 2003).

The positive predictive value (PPV) of a full cytogenetic analysis is 1.0 for numerical chromosome aberrations, meaning that there is complete certainty that the foetus has the chromosomal changes that are identified. Such a result will lead to an offer of further genetic counselling to the pregnant women and their partners. A negative answer means that the foetus does not have a common numerical aberration (National Board of Health, 2003). Due to the limited resolution of the chromosome analysis, however, a number of less common structural chromosome defects can be missed (personal communication Steen Kølvraa, FCMB, October 2006). It might also occur that abnormal cells are only confined to the placenta and not to the foetus (mosaicism), making clinical interpretation of the sample material difficult.

5. **Other developments in non-invasive prenatal diagnostic testing**

The literature indicates three major approaches in the development of a non-invasive prenatal diagnostic test: analysis of foetal cells in the maternal blood (the new FCMB test), determination of genetic mutations in circulating foetal genetic material in maternal plasma, and analysis of foetal cells from endocervical specimens (Simpson, 2005).

6. **Scenarios for the implementation of the FCMB test in Danish health care**

Implementation of the new FCMB test is dependent on a number of factors, including the performance of the test. This refers to the test’s sensitivity or detection rate (how good it is at correctly identifying abnormalities that are present), specificity (how good it is at correctly identifying the absence of abnormalities) and predictive value (the proportion of correct and incorrect diagnoses). Knowledge of these parameters is essential to realistically forecast the likely impact of the test, i.e. the extent to which it will replace alternative diagnostic procedures. Although such information is not yet available, it is expected by FCMB that the test when fully developed will be able to replace CVS and AC.

Three possible future scenarios for the test’s implementation are presented below. These scenarios were constructed on the basis of differing assumptions about the test’s performance, with assumptions ranging from an imperfect diagnostic test (Scenarios A and B) to a perfect test with 100% sensitivity and specificity (Scenario C). The scenarios were given to two experts (a clinical geneticist and a specialist in obstetrics and gynaecology) who were asked to comment on the likelihood of the test being implemented and the possible consequences.

The comparator used in the assessment of the FCMB test is current routine screening practice in Denmark that comprises the double test and nuchal translucency, with invasive diagnostic testing with CVS or AC in the event of a high risk for abnormalities.

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\(^4\) A trisomy is the presence of three, instead of the normal two, chromosomes of a particular numbered type in an organism.

\(^5\) Triploidy is the condition of some biological cells and organisms of containing three instead of two homologous sets of chromosomes.
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The triple test and ultrasound scanning for structural anomalies are not included in this comparator.

A. ‘Imperfect diagnostic test’ scenarios: add-on test in current screening practice

Scenario A - FCMB offered to high-risk pregnant women

Current first trimester screening (double test + NT) -> risk higher than or equal to 1:250 ->
FCMB test -> positive test result -> invasive technique

In this scenario, if current screening tests resulted in a risk for abnormality higher than or equal to 1:250, the FCMB would be offered; in the event of a positive FCMB test result, an invasive diagnostic test (CVS or AC) would be offered.

The experts were of the opinion that a woman who had been assessed on routine screening procedures as having a high risk of a child with a chromosomal abnormality would not accept a further test with sensitivity below 100%. She would be more likely to prefer karyotyping via a currently available invasive technique (CVS or AC), despite the associated risk of miscarriage.

One of the experts suggested, however, that if the FCMB test could decrease the risk to below 1:1000 it would be acceptable to most women.

According to the experts, their reactions reflect a wider discussion among health professionals involved in maternity care about preferring certainty versus increased sensitivity (but not to 100%). Those in favour of certainty in case of high risk women would not offer the ‘imperfect’ FCMB test, because to their opinion the next step should be to offer complete assurance to ‘high risk’ women about the outcome of the risk assessment. Those that are willing to compromise certainty would be willing to offer high risk women an additional ‘imperfect’ test if this test could further increase the sensitivity of the risk assessment, achieved through the double test and NT. The same discussion is likely to exist among pregnant women and their partners. Differing attitudes to the sensitivity of the FCMB test will influence acceptance of the test, and should therefore be further investigated (see recommendations).

One of the experts considered a disadvantage of the FCMB test to be that it provides less information (5 most common chromosomal abnormalities) than can be provided through CVS and AC (that can identify all chromosomal abnormalities). This concern was not shared by the other expert.

This scenario requires that health professionals are able to explain to pregnant women what the value of the additional FCMB test would be and how it would influence the detection rate of any abnormality, as well as make clear that some degree of uncertainty would still remain, which could only be removed by the carrying out of an invasive test.
Scenario B - FCMB offered to low-risk pregnant women

Current first trimester screening (double test + NT) -> risk lower than 1:250 -> FCMB test positive test result -> invasive technique

In this scenario, if current screening tests resulted in a risk for abnormality lower than 1:250, women would be informed about the possibility of having an additional test, the FCMB test, and in the event of a positive FCMB test result, an invasive diagnostic test (CVS or AC) would be offered. The women in the high risk group (risk > 1:250) would not be offered the FCMB test, but offered CVS or AC immediately. In scenario B, the additional ‘imperfect’ FCMB test will be used to increase the sensitivity of the test result for a group of low risk women, which have become worried or anxious after the first trimester screening, in order to provide further reassurance/more information.

Both clinicians considered this scenario to be more realistic to implement than scenario A. One of the clinicians suggested that women with a risk between 1:250 (or perhaps 1:100) and 1:1000 might benefit from the FCMB test. This scenario raises the discussion of what risk cut off point would be appropriate, as a selected cut off point is related to the detection- and false positive rate. The decision on which risk cut off points to select as boundaries for this scenario would be influenced by the final sensitivity and specificity of the test when clinically applied, as well as by attitudes of health care professionals and decision-makers. The rule of thumb in present day practice is that the false-positive rate should be below 5%. Another issue that would emerge is whether the test should be paid for by the state or by the pregnant women themselves. Both these issues would require further investigation (see recommendations).

B. Perfect diagnostic test scenario: substitution of current screening practice

Scenario C - FCMB test offered to all pregnant women

FCMB test replaces the current first trimester screening (double test + NT) in diagnosing the 5 most common chromosomal aberrations

Both experts would welcome such a test, but one of them noted that women should be made fully aware of the loss of information using the FCMB test compared to karyotyping based on CVS or AC. This expert considered that the willingness of women to accept this residual uncertainty (regarding less common abnormalities) would be an important factor for the general acceptance of the test. It was furthermore hypothesised that women would differ in this respect, with some being willing to unconditionally accept the tests offered to them by the health service, while others would be more likely to question standard screening procedures and would want to know the exact limitations of the test. The expert considered the loss of diagnostic information to be an important health policy issue as well, and requiring explicit decision making, for example by the National Board of Health.

The other expert expected (when asked) that less than 1% of women would still choose karyotyping based on CVS or AC after a negative FCMB test.
Conclusions of the scenarios testing:
- Scenarios A, B, and C would require a new communication strategy (about risk levels and the loss of information) targeted towards pregnant women and their partners, as well as new training material for relevant health care professionals
- Scenario B would require a discussion as to what risk cut-off point would have to be selected to ensure an acceptable (limited) number of false-positives
- Scenario B would require a discussion about whether the test should be offered for free by the state or paid for by the women themselves
- Scenario C would require a discussion at societal level about the consequences of the loss of information related to the new test.

7. Other factors influencing the implementation of the FCMB test

7.1. Women’s preferences for prenatal screening
In general, acceptance of prenatal testing seems to be related to parental reassurance, while the main reasons reported in the literature for declining screening relate to religious and moral arguments, arousal of feelings of anxiety and uncertainty, and the unreliability of a test (van den Berg et al., 2005). The uptake of prenatal screening tests is generally high in countries where prenatal screening is part of standard care, as it is in Denmark. Jørgensen (1995) earlier found an acceptance rate of about 80% for a second trimester serum test. Preference studies have shown that women prefer testing in the first trimester rather than in the second trimester (Bishop et al., 2004).

On this basis it can be assumed that if Danish women were offered the new FCMB test as part of routine screening, a very high percentage of them would accept the test because of its non-invasive character and the absence of a risk of miscarriage. The proportion of women who would not take the (imperfect or perfect) FCMB test in order to avoid being confronted with a decision involving termination of pregnancy can be assumed to be the same as the proportion of women who decline risk assessment with current screening tests.

7.2. Preferences of health care professionals
While pregnant women and health care professionals (such as obstetricians, midwives and clinical geneticists) have similar desires for optimal prenatal screening, they appear to differ in the value they attach to the timing of such tests (Bishop et al., 2004). It has been reported that women place less value on early tests than do health care professionals but greater value on a lower risk of miscarriage and higher detection rates. Health care professionals place a higher value on earlier tests because of the more beneficial timing of the possible undertaking of a provoked abortion. The results of this single study suggest that health professionals would be supportive of implementing the FCMB test as it can be carried out early in the pregnancy (and assuming that the assumptions about the test’s high detection rate proved to be true when it was introduced onto the market).

The FCMB test can be repeated without extra risk. As one expert noted, repeated testing with the FCMB test would only be useful in the event of technical error and would not influence detection rates.
7.3. Ethical aspects
Current screening services in Denmark have been organized to promote informed decision-making amongst pregnant women of all ages, as this was perceived to be lacking in the former system (in which prenatal diagnosis was offered only to women aged 35 years and older). A review of studies of women’s understanding of screening practices (Green et al., 2004) concluded, however, that most women do not make informed choices about screening. They found that, although women want to make informed choices about screening, women do not possess the required understanding of prenatal tests to be able to make an informed choice.
When prenatal screening is offered as part of routine care acceptance is typically perceived as self-evident and the uptake of screening is high (van den Berg, 2005). This may be at odds with a central objective of prenatal screening, which is to enable the pregnant women and their partners to make their own, informed decisions regarding acceptance of a screening test, as opposed to limiting as far as possible the number of children born with abnormalities (van den Berg et al., 2005).

The offer of the new FCMB test to all pregnant women may increase this conflict between potentially opposing objectives of screening. The new ‘perfect’ FCMB test would give Danish women an immediate (certain) diagnosis rather than the current risk assessment; some women will thus be more quickly confronted with a decision regarding termination of the pregnancy. It would become even more important for the screening programme to ensure that women understand the implications of potential test results, and that acceptance of prenatal testing is a result of a considered and conscious decision rather than simple compliance with standard procedures (van den Berg et al., 2005).

7.4. Organizational consequences
It is envisaged that the implementation of the new FCMB test would have the following organizational consequences:
• Greater centralization of invasive procedures (predominantly CVS)
• Shift of responsibility from biochemical departments to clinical genetics departments
• Purchase of new equipment for laboratory analysis
• Additional training of health professionals in genetic counselling
• Changes in information material for pregnant women and their partners

Centralization of CVS due to a decrease in the number of procedures
Implementation of the FCMB test would result in a reduced number of invasive diagnostic procedures (as CVS is the predominant test used in Denmark, AC is not included in the analyses that follow). To maintain quality standards of the CVS technique, it is likely that CVS services would need to be more centralized (one expert estimates that only two places would be needed in Denmark when scenario C would be implemented). This will lead to a discussion where these centres need to be situated geographically in Denmark, and will affect the distance that women would have to travel to get CVS.
Shift of responsibility from biochemical departments to clinical genetics departments
Whereas the current double and triple tests are analyzed in biochemical departments, the FCMB test would be analyzed in clinical genetics departments (similar to current practice with CVS and AC). Implementation of the FCMB test would thus have consequences for several professional groups, which could influence acceptance of the test.

Purchase of new analytical equipment
Analysis of the new FCMB test would require a high-speed, automatic microscope-based slide scanner that is not currently available in most Danish laboratories that analyze blood samples (personal communication, Steen Kølvraa). The price of this scanner is about 1 mio. DKK. Use of the scanner will require 2 days of additional training for laboratory staff (personal communication, Jesper Kielsgård, Brock & Michelsen, November 2006).

Additional training of health professionals responsible for genetic counselling
Implementation of the new FCMB test would require some additional training of health professionals involved in genetic counselling as the new test will have different performance characteristics in comparison to current screening and diagnostic tests, and will not provide the full spectrum of diagnostic information that can be obtained on the basis of CVS and AC. The additional training will involve clinicians and nurses, midwives and general practitioners.

Changes in information material for pregnant women and their partners
Implementation of the new FCMB test would also require changes in the information material about screening procedures that is currently provided to pregnant women and their partners.

8. Estimated budget impact of FCMB implementation

Budget impact – Scenario A
As scenario A was considered unrealistic by the experts (see paragraph 6 under A) it has not been further considered.

Budget impact – Scenario B
In scenario B (in which the FCMB test would be offered after current screening procedures to women with a risk lower than 1:250, but current practice with CVS for women with risk higher than 1:250 would be retained) the costs of implementing the FCMB test would be additional to the costs of current screening. There could also be cost savings from a reduced number of CVS procedures in this group, but this is not clear as it is not known how many women in the low risk group currently ask for CVS.

Costs of current screening:
Assuming an acceptance rate of 80% for the double test and NT (Würtz, 2005), and approximately 60,000 pregnancies a year (National Board of Health, 2005), there will be 48,000 women who will have the serum test (310 DKK per test) and the NT
ultrasound scans (286 DKK per scan). Annual costs of current screening with the double test and NT are thus approximately 29 mio. DKK.

Associated with current screening are the CVS procedures that are undertaken on the women found to have a risk higher than 1:250. In 2005, 975 CVS procedures were carried out for indications based on current screening practice (see Table 1). If full karyotyping is carried out, the cost of CVS is 4,141 DKK per procedure⁷, thus giving a cost of 4 mio. DKK for 975 CVS procedures. Current day practice often involves initial analysis by means of quick methods, i.e. providing faster results, such as by the FISH and PRC technique. Use of the FISH technique as well as the standard CVS analysis would increase the cost per procedure to 7,183 DKK (i.e. 4,141 + 3,042⁸). The total cost for 975 CVS procedures would then be 7 mio. DKK. If the PCR technique was used instead of FISH then the cost would be lower as this technique is less expensive.

Table 1 Number of 2005 Danish CVS procedures that diagnosed chromosome abnormalities in relation to the indication for investigation and the found abnormality (Fyns Amt not included)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total CVS undertaken</th>
<th>+21</th>
<th>+18</th>
<th>+13</th>
<th>+mar</th>
<th>XXY</th>
<th>XYY</th>
<th>XXX</th>
<th>X</th>
<th>Total anomalies diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk after double test or triple test</td>
<td>44</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ultrasound indicated high risk for Down’s syndrome</td>
<td>293</td>
<td>27</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>Ultrasound and biochemical markers (e.g. double test)</td>
<td>638</td>
<td>50</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>66</td>
</tr>
<tr>
<td>In total</td>
<td>975</td>
<td>78</td>
<td>16</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>113</td>
</tr>
</tbody>
</table>

Source: DCCR (information from Jan Hansen ahead of publication)

Additional costs of FCMB test:
The costs of implementing FCMB in this scenario are related to the cost of the additional FCMB tests and the costs related to extra CVS procedures undertaken as a result of the (imperfect) FCMB test.

The number of women that would have the FCMB test needs to be estimated. Based on illustrative figures in the report by the National Board of Health Working Group (see table 2), and an annual estimate of approximately 1,000 CVS procedures (based on table

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⁶ Costs of double test and NT scan are taken from a Fyns Amt report (http://bilag.fynsamt.dk/sy04/SHF/shf23novaapbil1.pdf#search=%22DRG%20takst%20CVS%22)
⁷ DRG takst 2006 – AC/CVS = 4,141 DKK.
1), it could be assumed that there are 1,000 women with a risk higher than 1:250 having CVS, and a further 3,000 with a risk lower than 1:250 but higher than 1:1000. Again assuming an acceptance rate of 80% for the FCMB test, then at least 2,400 (i.e. 3,000*0.80) women will have the FCMB test. With a unit cost of 47 DKK per FCMB test (excl. e.g. personnel costs), the costs from administering the test would be approximately 113,000 DKK.

**Figure 4 Relation between number of invasive diagnostic tests (antal invasive) and number of diagnosed cases with Down syndrome (antal DS)**

Implementation of the FCMB test would also have consequences in terms of investment costs and operating costs, as outlined below. These are not costed in detail here, but the set up costs would be at least 1.5 mio. DKK, of which 1 mio. DKK accounts for the cost of the slide scanner. Investment costs would amongst others include: a high-speed, automatic microscope-based slide scanner (MetaSystems), equipment for magnetic cell sorting (MACS), autostaining capability, and new information material to health professionals and pregnant women and their partners. The equivalent annual cost over a period of 10 years, and an interest rate of 0.05 will be 194,000 DKK.

The operating costs would include e.g. maintenance of the slide scanner, the number of blood samples analyzed per year, and preparation & processing of slides (no. per year).

The total annual cost of Scenario B would be approximated by:

<table>
<thead>
<tr>
<th>Costs</th>
<th>Total (mio. DKK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs of current screening + invasive testing</td>
<td>29.0 + 7.0</td>
</tr>
<tr>
<td>Costs from FCMB testing</td>
<td>113,000 + 194,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36.307.000</strong></td>
</tr>
</tbody>
</table>
Budget impact – Scenario C
Scenario C involves the replacement of current screening procedures (the double test and NT) with the new FCMB test. The costs associated with this scenario are thus the costs of implementing the FCMB test offset by the savings from elimination of the current screening tests.

Costs of implementing FCMB test:
Again assuming an acceptance rate of 80% for the FCMB test, and approximately 60,000 pregnancies a year, there will be 48,000 women who will have the FCMB test. At 47 DKK per test, this will amount to 2.2 mio. DKK. Adding to this the equivalent annual costs of 194,000, the costs of implementing FCMB test as first-line screening is estimated to be 2.4 mio. DKK.

Cost savings from replacement of current screening tests and invasive tests:
Cost savings in this scenario arise from two sources: i) elimination of the current double test and NT scan, and ii) elimination of later invasive tests for women with positive screening results.
i) Assuming an acceptance rate for both tests of 80% and 60,000 pregnancies a year, 48,000 women would no longer have the serum test (310 DKK per test) and NT scan (286 DKK per test). The associated cost saving would thus be approximately 29 mio. DKK.
ii) Again assuming 975 CVS procedures annually at 7,183 DKK per procedure (including FISH analysis), the cost savings from avoided CVS procedures would be 7 mio. DKK.

The total cost of Scenario C is thus:

<table>
<thead>
<tr>
<th>Costs</th>
<th>mio. DKK</th>
<th>Total (mio. DKK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs of implementing FCMB test</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Cost savings</td>
<td>29.0 + 7.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Overall savings (approximately)</td>
<td></td>
<td>33.6</td>
</tr>
</tbody>
</table>

9. Cost-effectiveness of the FCMB test compared to current screening

Health care interventions (including new diagnostic tests) can be visualized as lying in a quadrant of a cost-effectiveness plane (Drummond et al., 2005) (see Figure 1). This plane is divided into four quadrants that describe four possible situations in relation to the additional costs and outcome effects of a new intervention (e.g. the FCMB test) compared to the standard therapy (e.g. the current screening programme).

In such a diagram, the horizontal axis represents the difference in effect between the intervention and the relevant comparator treatment, while the vertical axis represents the difference in cost (Drummond et al., 2005). For a new test, the optimal result would be a cost-effectiveness ratio that lay in the south-east quadrant of the diagram (point C, i.e. point C, i.e. 

\[ \text{Costs of double test and NT scan are taken from a Fyns Amt report (http://bilag.fyns-amt.dk/sy04/SHF/shf23novaapbil1.pdf#search=%22DRG%20takst%20CVS%22)} \]
cheaper and more effective); it would then be an easy decision for policy-makers to recommend uptake of the new technology, which is both cheaper and more effective than the current treatment (all other considerations being equal). If, on the other hand, the new technology was more effective but also more expensive than current treatment (for example represented by point A in the north-east quadrant of the diagram), then it is helpful to define a maximum acceptable value for the cost-effectiveness ratio. This ceiling value can then be used to judge whether or not the new technology is cost-effective.

Cost-effectiveness analyses would need to be conducted for all the scenarios outlined here. It is likely, however, that the cost-effectiveness ratio for the FCMB test used as in scenario B would lie in the north-east quadrant (i.e. more effective but also more costly than the current screening programme). The extra cost of this scenario would depend on a number of factors, e.g. the proportion of women with a risk between 1:250 and 1:1000 who would (still) choose CVS after the FCMB test in order to obtain more complete foetal karyotyping.

For scenario C, the cost-effectiveness ratio for the FCMB test is likely to lie in the south-east quadrant, as the test would be more effective and less costly than the current screening programme. It can be noted that replacement of the current screening programme with the (perfect) FCMB test would also eliminate provoked abortions due to invasive diagnostic techniques.

![Cost-effectiveness plane](image)

Figure 5 Cost-effectiveness plane (taken from Stein K. Economic Evaluation, presentation)
10. **Recommendations for further study**

- A survey among pregnant women and health professionals to study acceptance of the FCMB test with a sensitivity below 100% as an add-on test in current screening in relation to invasive diagnostics with 100% sensitivity and a risk of miscarriage (Scenario A, B, and C)
- Survey among pregnant women and health professionals to study acceptance of the FCMB test, and the related loss of diagnostic information in relation to the possibility of full diagnostic information with invasive diagnostics (Scenario A, B, and C)
- A study among the general public and health care decision makers on acceptance of public reimbursement of the FCMB test for the low risk group of pregnant women (Scenario B).
- A willingness to pay study among pregnant women in the low risk group (Scenario B)
- A study focusing on the consequences of the loss of information on societal level connected to the FCMB test compared to the full diagnostic information based on CVS and AC.
11. References


FCMB. Introduction to FCMB market and technology, June 9th, 2006.


Early assessment of an emerging test for non-invasive prenatal diagnosis


