Review of Rapid Fetal Fibronectin Assay in the Management of Suspected Preterm Labour

Review # 4
AHTDP# 03-13

June 2006

Prepared by:
Charis Management Consulting Inc.

Based on reports from:
Alberta Heritage Foundation for Medical Research, and
Institute of Health Economics
This report has been prepared to support and inform the decision-making of Alberta Health and Wellness and its stakeholders regarding the provision of health technologies in Alberta’s health care system and is based on the information available from public literature, expert opinion, and other sources at the time of preparation. Its conclusions are solely those of the review group and do not represent the policies or position of the Government of Alberta, Alberta Health and Wellness or any other agency.

For more information contact:

Health Technologies and Services Policy
Program Services Division
Alberta Health & Wellness
P.O. Box 1360 Stn Main
Edmonton, Alberta
Canada T5J 2N3

Other reports can be found on the Alberta Health and Wellness website:

www.health.alberta.ca

ISBN # 978-0-7785-6063-0
Executive Summary

- The fetal fibronectin (fFN) assay is a laboratory test used when women present with symptoms of preterm labour (PTL); a negative result rules out the possibility of delivery in the next seven to 14 days. The objective of the fFN test is to accurately identify symptomatic women with false PTL to avoid providing unnecessary care (hospitalization and medication administration) and ambulance transfer.

- Current practice without fFN test availability involves diagnosis through clinical history and physical examination. If the physical examination does not immediately confirm a diagnosis of progressive PTL, the symptomatic woman is usually hospitalized for a period of observation to determine if the symptoms subside or progress. During this time, bed rest and possible treatment in the form of antibiotics or tocolytic drugs may be prescribed, depending on the symptoms and results of the examination. Clinical diagnosis, however, is often unreliable and results in over-diagnosis of PTL. In addition to clinical diagnosis, various methods for diagnosing preterm labour have been tried; however, fFN has received the most extensive evaluation in the peer reviewed literature.

- It is estimated that 80 percent of women with spontaneous preterm labour (PTL) without the rupture of membranes will go on to deliver their babies at full term - that is, they present with false PTL. It is estimated that care of such women resulted in nine instances of potentially avoidable air ambulance transfers in Alberta in 2004/05 and between 9 and 13 potentially avoidable ground ambulance transfers during the same period.

- Seventy one hospitals in Alberta are listed as having maternity services. They are classified into three categories of perinatal care, with Level 1 hospitals providing care to healthy mothers and babies, Level 2 having the capacity to care for certain complications, and Level 3 representing tertiary care hospitals housing the most specialized perinatal staff and equipment. The Calgary Health Region has undertaken a pilot study of the fFN test, and based on positive results, implemented the test in its level 2 and 3 hospitals. A pilot study was also conducted in the Capital Health Region’s level 3 hospital but, the fFN test has not been fully implemented in this region.

- Evidence from the literature suggests that the negative predictive value of the fFN test does aid in ruling out unnecessary interventions and preventive therapy for women with symptoms of PTL. Evidence from observational studies reported in the literature also suggests that fFN testing has a theoretical potential, based on its high negative predictive value, to reduce health care utilization and unnecessary treatment for these women. However, for the most part this potential has not been confirmed, in experimental randomized controlled trial (RCT) studies conducted to date. In order for this potential to be realized, physicians must change their practice patterns when test results are negative. If physicians continue current patterns of care when results are negative and increase interventions when results are positive, resource utilization may actually increase.

- A cost analysis undertaken as part of this review indicates a potential net savings to the provincial health system if fFN testing was universally introduced; however, the net savings would be greatest if fFN testing was introduced only in Level 2 and 3 hospitals. The cost of introducing the test would be offset by the value of reductions in length of
hospital stay. Introduction in Level 1 hospitals results in a net cost to these hospitals as the costs of introducing the test would not be offset by the cost savings, even when air and ground ambulance transfer avoidance is considered. This net cost is largely explained by the need for hospitals delivering less than 1000 babies per year to purchase or rent the fFN testing hardware. These units are provided free of charge to hospitals delivering more than 1000 babies annually. The cost of the TLi IQ instrument including service, replacement and training costs is $2,668 (Cdn) per unit.

- Four policy options were identified and are described in the synthesis report:
  1. Do not provide fFN testing in Alberta.
  2. Provide fFN testing in Level 2 and 3 hospitals only.
  3. Provide fFN testing in all Level 1, 2 and 3 hospitals.
  4. Provide fFN testing in all Level 2 and 3 hospitals and in selected Level 1 hospitals based on proximity to Level 2 and 3 hospitals and number of births per year.
# Table of Contents

Introduction ...........................................................................................................................1  
Objectives of Review .............................................................................................................1
Alberta Health Technologies Decision Process ........................................................................1
Fetal Fibronectin Testing In Alberta ....................................................................................2
The fFN review project .........................................................................................................2
Outline of Report ...................................................................................................................3
Preterm Labour (PTL) .........................................................................................................3
Social and System Demographics .......................................................................................4
  Current Patterns of Care ..................................................................................................5
  System Capacity .............................................................................................................6
Technology Effects and Effectiveness ................................................................................7
  Fetal Fibronectin Assay ................................................................................................7
  Conditions for Use .......................................................................................................8
  Effectiveness ..................................................................................................................8
  Risk to Patient or Fetus ...............................................................................................9
Cost Analysis .......................................................................................................................9
Policy Considerations .........................................................................................................11
  Legislative and Policy Framework ...............................................................................11
  Fit With Current Directions and Principles of Alberta’s Health System .......................11
  Other Canadian Jurisdictions ......................................................................................12
  Potential Effect of Decision .......................................................................................12
  Potential for Transfer of Service and Funds ...............................................................13
Summary and Policy Options ..............................................................................................14
  The Three Screens .....................................................................................................14
  Policy Options .............................................................................................................16
Appendix A: .........................................................................................................................18
  List of Analysis Reports ............................................................................................18
Appendix B: .........................................................................................................................19
Introduction

This report summarizes the findings and conclusions of a review to determine whether public funding should support the use of fetal fibronectin (fFN) testing in the management of suspected preterm labour.

Objectives of Review

The review of fFN testing was undertaken as part of the Alberta Health Technologies Decision Process (AHTDP) with the objectives of reviewing the:

1. Effectiveness of fFN testing; and
2. Fiscal considerations for the provision of fFN testing.

Alberta Health Technologies Decision Process

In March 2003, the Expert Advisory Panel Reviewed Publicly Funded Health Services (“the Expert Panel”) submitted its report The Burden of Proof recommending a three-screen decision framework for the assessment of new technologies, along with the creation of an independent review agency. The three screens, along with their associated questions are:

1. Technical
   - Is the technology safe?
   - Is it effective?
   - Is it cost-effective?

2. Socio-economic
   - Is it important for re-distribution?
   - What is the impact on specific populations?
   - Do other service options exist?
   - Do other payment options exist?
   - Is there alignment with regulatory and policy frameworks?

3. Fiscal
   - Is the technology affordable within the current budget?
   - Would it be affordable with the elimination of existing, less cost-effective treatments?
   - Would it be affordable only with new funding or revenue?

The government accepted the Expert Panel’s recommended review process in principle and determined to strengthen existing processes to improve the rigor and timeliness of decisions. The process would be implemented incrementally with stakeholders including the health authorities, the Alberta Medical Association and the Alberta Heritage Foundation for Medical Research (AHFMR). In September 2003, the Health Technologies and Services Policy Branch was established to coordinate the development and implementation of the Alberta Health Technology Decision Process.
The full process involves eight broad phases or steps. Several steps have significant stakeholder involvement. Step 1 concerns setting priorities. Once fully implemented, it will see stakeholders canvassed annually to identify technologies needing review. A representative advisory committee will prioritize these technologies for review based on established criteria. Steps 2 and 3 cover internal government processes culminating in the project plan for a review of an identified technology.

Step 4, conducting the review, gathers and reviews the evidence and information required for the application of the three-screen process recommended by the Expert Panel and involves a broad range of stakeholders and agencies, such as the (AHFMR), the Institute for Health Economics (IHE), the University of Alberta and the University of Calgary, as well as, medical and policy experts from relevant areas of the health system. In Step 5, consulting and formulating advice, health system decision makers and other stakeholders at all levels are consulted on the results of the reviews before recommendations are finalized and submitted to government for approval (step 6). In Step 7, the health system community is again significantly involved in implementing the decisions. The final step, scheduled reviews, recognizes that follow-up reviews are required to maintain up-to-date evidence related to the technology.

**Fetal Fibronectin Testing In Alberta**

The fFN assay is a diagnostic laboratory test used for women with symptoms of PTL to rule out the possibility of delivery in the 7 to 14 days following the test. The test was introduced in the Calgary Health Region in 2002 as a pilot, and because of the positive outcomes of the pilot, fFN testing has been implemented in all level 2 and 3 hospitals, where it is routinely used. A pilot has also been conducted at the Level 3 hospital in the Capital Health Region. Results indicated a decrease in the length of hospital stay (LOS) without adverse impact on premature delivery. The Capital Health region has not yet implemented routine fFN testing.

**The fFN review project**

The review consisted of four components:

1. Social and system demographics with a focus on the population characteristics of women presenting with PTL and current patterns of care;
2. Technology effects and effectiveness analysis;
3. Cost analysis; and
4. Policy analysis.

The social and system demographics and economic analysis was conducted by a researcher from the IHE. The analysis of technology effects and effectiveness was conducted by staff of the Alberta Heritage Foundation for Medical Research Health Technology Assessment Unit. Each of these teams completed their own reports which are available under a separate cover (Appendix A). The findings contained in those reports served as a basis for completion of this synthesis report.

The analyses were coordinated with the assistance of a project manager and an Expert Advisory Group established by the Health Technologies and Services Policy Unit of Alberta Health and Wellness. Appendix B provides a listing of all project team and Expert Advisory Group members.
Outline of Report

In subsequent sections of this Synthesis Report, the technology and condition it is expected to address are presented. They are followed by the findings from each of the four project components and the review analysis and summary.

Preterm Labour (PTL)

The Society of Obstetricians and Gynecologists of Canada (SOGC) defines PTL as “the demonstrated progressive change of the cervix with uterine contractions occurring between 20 and 36 completed weeks of gestation”\(^1\) (p. 2) and reports Statistic Canada data suggesting a steady increase in PTL rates in Canada between the years 1991 and 2000. Important factors contributing to this rising rate are young maternal age, older maternal age, smoking, multiple pregnancies and history of PTL. Infections and stress may also contribute to the risk of PTL.

Preterm birth (PTB) is considered to be the most important cause of perinatal mortality and morbidity accounting for up to 75 percent of preventable perinatal mortality.\(^2\) Preterm babies who survive are at high risk for long-term morbidity, including neurodevelopmental problems such as cerebral palsy, respiratory, hearing, vision and other health conditions. PTB is projected to cost the Canadian health care system approximately $13.3 billion annually.\(^3\)

Preterm rates in Alberta are higher than the national rate. In 2004, almost nine percent of Alberta’s 40,581 births were preterm. PTB can result from spontaneous labour with or without premature rupture of the membranes, or it can result from intervention induced by fetal or maternal complications.

Approximately 80 percent of women with spontaneous PTL without the rupture of membranes will go on to deliver their babies at full term. The challenge for clinicians is to correctly identify those women who are in true PTL and will deliver prematurely in order to provide appropriate care, and conversely to not provide unnecessary care to those who are not in true PTL. The objective of early diagnosis of true PTL is transfer to an appropriate tertiary centre. Women may receive corticosteroids to help maturation of the neonatal lungs and/or antibiotics or tocolytics to prolong pregnancy.

\(^2\) Ibid, p. 2.
\(^3\) Ibid, p. 2.
Social and System Demographics

This review considered three questions under the social and system demographics component:

1. What are the population dynamics of patients presenting with symptoms of PTL?
2. What are the current patterns of care related to this technology?
3. What is the capacity of Alberta’s health system related to this technology?

Population Dynamics

Data reported in this section are from the provincial in-patient, ambulatory care and physician databases for the years (2004/05). It is noted that during this time period, the Calgary Health Region had already implemented fFN testing, and the Capital Health Region conducted their pilot from June 15, 2004 through February 15, 2005.

Number of women

In the fiscal year 2004/05, a total of 1,247 women were diagnosed with threatened PTL in either an outpatient or inpatient setting in Alberta. This represents about three percent of the approximately 41,000 births annually. Of the 1,247 women, 359 were admitted to hospital for PTL. In addition, 846 PTBs occurred in women who never had an episode of threatened PTL, and another 291 who had a diagnosis of PTL delayed by therapy with 280 admissions. Thus, a total of 2,394 women may have presented to the system with symptoms of PTL, representing 5.9 percent of all births in 2004.

Seventy-three percent of women with threatened PTL went on to give birth at term (≥ 37 weeks) and 27 percent gave birth prematurely, including four percent who were moderately premature (between 28-32 weeks) and one percent who were extremely premature (between 20-27 weeks). The average gestational age for the women with threatened PTL was 31 weeks.

Geographic distribution

Thirty-one percent of women with inpatient admissions for threatened PTL were from Calgary Health Region and 28 percent from the Capital Health Region. In 2003, the Calgary Health Region accounts for 36 percent of all live births and 38 percent of PTBs, while the Capital Health Region accounts for 29 percent of all live births and 31 percent of PTBs. Outside of the Calgary and Capital Health Regions, the regions of residence for women with threatened PTL, in order of frequency were: Aspen, David Thompson, Peace Country, East Central, Northern Lights, Palliser and Chinook.

Outside of the Calgary and Capital Health Regions, the regions of residence for women with threatened PTL who were admitted as inpatients, in order of frequency, were: David Thompson, Aspen, Peace Country, Palliser, East Central, Northern Lights and Chinook.

---

Age and socio-economic structure

The average age of women presenting with PTL was 27.3 with the youngest being 15 and the oldest being 44. This compares with an average maternal age of 29 years for all births in Alberta in 2003. The average age of women in the study sample giving preterm birth at 30 years (youngest being 14 and oldest being 46).

The average maternal age for the PTL sub-sample was found to be youngest in the Chinook Regional Health Authority at 24.6 years and oldest for the Palliser Regional Health Authority at 28.3 years.

Of the 1,247 women with PTL in the study sample, 10 percent were aboriginal, 16 percent received premium support and nine percent were on welfare. This reflects an over-representation of aboriginals and those on income support for women with threatened PTL when compared with the general female population between 13 and 50 or with the distribution of children under the age of one.

Current Patterns of Care

Although PTL is diagnosed by uterine activity and cervical change, there are currently no uniformly accepted standards for defining PTL. Clinical symptoms suggesting PTL are uterine contractions, low abdominal pain, low backache, pelvic pressure, increased vaginal discharge and bleeding or spotting. However, contractions may be more or less regular, painful or painless and are distinguished from the contractions of term labour only by their persistence. Signs of PTL include cervical effacement and dilation.

PTL is diagnosed by clinical history and physical examination. Initial cervical dilation of \( \geq 3 \) cm and at least 80 percent cervical effacement are strongly associated with PTB within the next 24 hours to 7 days. If possible, these women are aggressively treated to delay delivery.

If the physical examination does not immediately confirm a diagnosis of progressive PTL, the symptomatic woman is usually hospitalized for a period of observation to determine if the symptoms subside or progress. During this time, bed rest and medications may be prescribed, depending on the symptoms and results of the physical examination.

Clinical diagnosis, however, is often unreliable and results in an over-diagnosis of PTL. Women often have contractions without cervical change making a diagnosis difficult. When the cervix is dilated <3 cm, the diagnosis of true PTL is more difficult to establish. The literature suggests that because early signs and symptoms are non-specific and can occur in term pregnancies, false positive diagnoses on strictly clinical criteria run as high as 50 percent, and true PTL may be missed in 15 to 20 percent of cases.

Various methods of diagnosing PTL have been used, including risk factor scoring systems, assessment of the cervical changes by ultrasound examination, home uterine activity monitoring, tests for genital tract inflammation and vaginal infection and detection of various biochemical markers (including fFN) in cervicovaginal secretions, blood and saliva. Of these, fFN has received the most extensive evaluation in the peer reviewed literature over the last 10 years.

---

System Capacity

Hospitals with maternity wards are classified into three categories in Canada, as defined by the Public Health Agency of Canada. Level 1 hospitals are those providing care for healthy mothers and babies or those with few complications. The hospitals will have procedures for emergency response, which may include transfers to hospitals with greater capacity for perinatal care. They are generally, but not exclusively, located in rural centres and have fewer than 1000 births annually. In Alberta in 2004, 61 such hospitals recorded births.

Level 2 hospitals are hospitals with more advanced capacity and equipment for perinatal care. According to national guidelines, they should have the ability to care for pregnant women at ≥32 weeks gestation who may experience certain complications. Direct access to specialty consultations from obstetricians and pediatricians should be available. In the non-metro regions, these are generally the regional hospitals. Alberta has eight Level 2 hospitals: Chinook Regional Hospital in the Chinook Health Region, Medicine Hat Regional Hospital in the Palliser Health Region, the Peter Lougheed Centre and Rockyview General Hospital in the Calgary Health Region, Red Deer Regional Hospital in the David Thompson Health Region, the Grey Nuns and the Misericordia community hospitals in the Capital Health Region, and the Queen Elizabeth II Hospital in Peace Country Health.

Level 3 hospitals are tertiary care centres housing the most specialized perinatal health staff and equipment. According to national guidelines, tertiary centres have the capacity to care for women whose pregnancies may be at risk; for example, those <32 weeks gestation or having severe medical complications. There is direct access to subspecialty consultants such as maternal/fetal medicine specialists and neonatologists. There are two such centres in Alberta, located at the Foothills Medical Centre in Calgary and the Royal Alexandra Hospital in Edmonton.

Most women with threatened PTL are transferred to Level 2 or 3 hospitals for care because of the greater capacity of these hospitals to respond to perinatal complications and to provide specialized neonatal care. Transfer from Level 1 or 2 hospitals to either Level 2 or 3 hospitals is accomplished through Alberta’s air and ground ambulance system delivered through a variety of funding arrangements. Alberta Health and Wellness directly contracts with fixed-wing aircraft operators and with the Calgary and the Capital Health Regions for rotary-wing (helicopter) services. In turn, the two metro-regions contract with STARS air ambulance for the rotary-wing services.

The provincial health region population-based funding formula includes dollars for the provision of inter-facility transfers. In addition, Alberta Health and Wellness directly funds municipalities in seven health regions for ground ambulance services. Alberta Health and Wellness provides funding to the other two regions (Palliser and Peace Country) to directly provide or contract ground ambulance services. User fees may be charged for ground ambulance services which users pay out-of-pocket or through a supplementary health insurance plan, such as Alberta Blue Cross. Alberta Health and Wellness operates the Blue Cross program that annually spends about $18 million on ground ambulance services for seniors and others who have purchased non-group coverage.

Diagnostic medical laboratory services are offered by independent providers under contract with each regional health authority (RHA). Since fFN testing is a new technology and does not appear to be widely available at this time, the need for this testing in Alberta is not immediately apparent. The decision process will need to consider the potential benefits and costs of this test before deciding whether to include it as a covered benefit under the RHA's funding arrangements. The decision process should also consider factors such as the availability of appropriate laboratory equipment and personnel, and the need for ongoing monitoring and quality assurance in order to ensure accurate and consistent testing results. If the need for fFN testing is determined to be justified, the decision process will need to identify the appropriate funding mechanism for this service.
not replace an existing laboratory test, the introduction of fFN testing presents resource, training and quality assurance, implications for laboratory and/or RHA personnel depending on each RHA’s decision to place the unit in a central laboratory or at point-of-care.

**Technology Effects and Effectiveness**

Four questions are addressed under this component:

1. What is the action of the technology?
2. What are the conditions for which the technology should be used?
3. What is the test’s effectiveness?
4. What are the risks to the patient and fetus from the test itself?

**Fetal Fibronectin Assay**

The fFN assay is a membrane assay that uses a system for rapid detection of fFN and manufactured under the trade name *Rapid fFN for TL‡ System*, sometimes referred to in this document as rapid fFN assay.

The fFN is a glycoprotein produced by many cell types, including those of the fetal amnion (membrane). It is found in high concentrations in amniotic fluid and throughout the membrane structure. Although its specific function remains unknown, it is believed that fFN may have a role in implantation and placental-uterine attachment.

In normal pregnancies, fFN levels are high for the first 20 to 22 weeks, then fall to very low levels, and rise again as the pregnancy approaches term. However, fFN is not normally detectable (at high levels) in cervicovaginal secretions between the 22nd and 37th week of gestation, and particularly before the 35th week of gestation. Its presence at high levels during this period may indicate disruption of the utero-placental interface. It is not clear what causes cervicovaginal fFN levels to increase prematurely in women at risk of preterm delivery. fFN can be detected and measured in the cervicovaginal secretions by a laboratory test that uses a specific monoclonal (FDC-6) antibody.

The fFN assays that have been used in the clinical studies published to date have been manufactured by Adeza Biomedical Corporation in Sunnyvale, California. An early version of the test called the ELISA method (Enzyme-Linked Immunosorbant Assay) was licensed in North America in 1995. It has been discontinued because it was found not to be practical for routine rapid testing deemed critical for diagnosing PTL in symptomatic patients. The ELISA has been replaced with the rapid fFN assay which is the only modality of fFN testing currently available on the market in North America.

The rapid version of the fFN test is a lateral-flow, solid-phase immunosorbent assay device designed to qualitatively detect fFN in cervicovaginal specimens collected with the Adeza Biomedical Specimen Collection Kit. A vaginal swab is used to collect the specimen. Specimens are mixed in a collecting tube containing an antibody/gold colloid conjugate. The mixture is then passed through a membrane coated with the monoclonal FDC-6

---

8 Taken from Corabian P & Harstall C. (2006). *The role of rapid fetal fibronectin assay in the management of suspected preterm labor.* Edmonton: Alberta Heritage Foundation for Medical Research. The reader is encouraged to access the full report for more comprehensive presentation of this information.
antibody. If the specimen contains fFN, it will adhere to the membrane and the gold will create a visible spot on the membrane.

Once the sample is collected and received at the testing site - either a central laboratory or a labour and delivery unit - the assay takes approximately 30 minutes, including data entry into the TLJ\textsuperscript{TM} system and verification of acceptable quality control. Upon completion, the TLJ\textsuperscript{TM} system automatically prints and displays the result as positive or negative (fFN level of $\geq 50$ ng/ml is a positive result and $\leq 50$ ng/ml is a negative result). The total time from specimen collection to clinician reporting the results to the patient can be accomplished within two hours.

The TLJ\textsuperscript{TM} IQ instrument currently used replaces an original unit called the TLJ\textsuperscript{TM} analyzer and has simplified quality control. The IQ instrument eliminates the need for daily calibration and daily performance of a liquid quality control as it routinely self verifies both IQ instrument quality control and liquid controls as acceptable. If the TLJ\textsuperscript{TM} IQ instrument or reagent quality control fails, the instrument notifies the operator with error codes. The manufacturer reports that measurements done with the TLJ\textsuperscript{TM} IQ instrument can be and have been performed in a central or hospital laboratory or at the bedside. It is recommended to be used near the patient test site.

**Conditions for Use**

Health Canada advises that both the older ELISA and the Rapid fFN for the TLJ\textsuperscript{TM} system manufactured by Adeza Biomedical Corporation are licensed as an aid in assessing the risk of preterm delivery in <7 or <14 days from the time of sample collection in pregnant women with signs and symptoms of early PTL.

The U.S. Food and Drug Administration (FDA) has cleared the use of both devices as an aid in assessing the risk of preterm delivery in $\leq 7$ or $\leq 14$ days from the time of sample collection in pregnant women with signs and symptoms of early PTL. Intact amniotic membranes and minimal cervical dilation (<3 cm) sampled between 24 weeks 0 days and 34 weeks 6 days gestation. The American College of Obstetricians and Gynecologists (ACOG) recommends fFN testing only for symptomatic women with high-risk pregnancies where PTL is suspected and clinical criteria matching those of the FDA are met.

The FDA further approves the use for fFN testing in conjunction with other clinical information as an aid for rapidly assessing the risk of preterm delivery in $\leq 34$ weeks 6 days when a cervicovaginal sample is obtained during a routine prenatal visit between 22 weeks 0 days and 30 weeks 6 days of gestation in women with a singleton pregnancy.

Health Canada and the FDA recently provided supplemental approval for the Rapid fFN for the TLJ\textsuperscript{TM} system using the IQ instrument.

**Effectiveness**

Published systematic reviews address the question of diagnostic performance of the rapid fFN assay. The primary source of evidence within these systematic reviews is from observational studies (prospective and retrospective cohort studies) in which the fFN specimens were obtained and tested. In most of these studies the clinical staff was blinded to the test results and managed the suspected PTL cases according to standard protocols. These studies, however, did not document the usefulness of the test in terms of patient outcomes.
The evidence supports that the negative predictive value (NPV) of the fFN test does aid in ruling out unnecessary interventions and preventive therapy for symptomatic women before 34 and 37 weeks of gestation, with singleton gestation, intact membranes, and cervical dilation of <3 cm. The NPVs calculated for specific time intervals indicate that approximately one percent of women in this population will deliver prematurely within the two weeks (14 days) following the fFN specimen collection.

There are several Canadian studies (of which only one was published) that investigated the impact of using the rapid fFN assay on patient outcomes, resource usage and health care costs associated with the management of suspected PTL in symptomatic women. The reported results suggest that knowledge of a negative rapid fFN test result may help to avoid over-diagnosis of PTL and use of unnecessary interventions. Negative neonatal outcomes are not reported with the incorporation of the rapid fFN testing as an aid in diagnosing suspected PTL. However, these studies utilized historical controls for comparison, if they made any comparisons. The use of historical controls is a major study design flaw and may have resulted in selection bias. Changes in physician practice patterns may also have influenced the assessed outcomes.

Further assessment using well-designed studies is needed to better understand whether and under what circumstances the predictive characteristics of the rapid fFN assay can be translated into a better clinical practice resulting in improved patient outcomes and reduced resource usage.

### Risk to Patient or Fetus

According to the reviewed literature, manufacturer and expert opinion, there is little risk to the patient due to performing the procedure itself. There is no more risk to the patient in performing the rapid fFN assay than with performing a Pap smear test.

Harm to the mother and/or infant can be caused by treatments that may follow a false positive fFN test result. The added psychological stress for the patient and the use of additional resources to monitor a predicted development of PTL are undesirable outcomes. Another risk is that of withholding appropriate interventions due to false negative test results.

Clinicians considering the use of the rapid fFN assay are cautioned that any modifications of the assay protocol, as described by the manufacturer, may yield erroneous results.

### Cost Analysis

A cost analysis was undertaken to address the questions: Does fFN testing have a net positive effect on health system costs? Do costs avoided in unnecessary hospitalizations and transportation outweigh the incremental costs of the test?

Results from a literature review undertaken in this component suggest that fFN has a potential to reduce health care utilization and unnecessary treatment by more accurately identifying women who are not in true PTL. Theoretical potential is suggested by the high negative predictive value and effectiveness results from observational studies using historical

---

9 From Currie G. (2006). *Fetal fibronectin testing for the diagnosis of pre-term labour in symptomatic women: an analysis of cost implications for Alberta.* Institute for Health Economics. The reader is encouraged to access the full report for more comprehensive presentation of this information.
controls. The literature supports the importance of establishing a protocol for the use of fFN results in the management of PTL. Initial and ongoing education and audit of physician practice are required to ensure this potential is realized. If physicians do not discontinue their traditional interventions when negative test results occur and increase their interventions with a positive test result, then it is likely that resource use will actually increase.

For the most part, the potential to reduce health care utilization and unnecessary treatment has not been confirmed in the experimental (RCT) studies that have been conducted. However, these RCTs did not incorporate explicit protocols for positive and negative fFN management or demonstrated educational interventions. Knowledge translation is a key component of these RCTs; although, this was not fully addressed by any of the trials. This may explain limited impact of fFN testing in terms of change in clinical practice regarding the management of PTL.

The published literature considers the impact of fFN testing available in referral tertiary hospitals where admissions (or transfers) for care for PTL would occur. The impact of fFN testing outside these settings has not been examined in the published literature.

The cost analysis undertaken as part of this project suggested a potential for cost savings to the provincial health system with the introduction of fFN testing. This ability to offset costs is greatest if the test was to be introduced in Level 2 and 3 hospitals only, primarily through reduced LOS. If the test is also introduced to Level 1 hospitals, then the net overall savings to the system are reduced, despite potentially avoided air and ground ambulance transfers.

Costs associated with introducing fFN testing in Level 1 hospitals would not be offset by the value achieved through reduced LOS and avoidance of air and ground ambulance transfer costs. A net loss for Level 1 hospitals is largely explained by the need for hospitals delivering less than 1000 babies per year to purchase or rent the fFN testing hardware. These units are provided free of charge to hospitals delivering more than 1000 babies per year. It is noted that there is little evidence in the literature on the use of fFN testing in Level 1 hospitals.

It is estimated that in 2004/05 fFN testing would have resulted in nine instances of potentially avoidable air ambulance transfers, between 9 and 13 potentially avoided combined air/ground ambulance transfers, and 43 potentially avoided ground transfers. Most of the ground ambulance transfers would be within region; 19 of 43 would involve between region transfers.

The cost of the TLi IQ instrument including service, replacement and training costs is $2,668 CDN per unit. Only one would be needed per hospital. The variable costs are estimated at $100 per test administration.
Policy Considerations

Legislative and Policy Framework

In 1995, the Alberta government undertook a restructuring of medical diagnostic laboratory services. At that time, laboratory testing was removed from the standard fee codes in the Schedule of Medical Benefits (under the Alberta Health Care Insurance Act). Correspondingly, Alberta Health and Wellness transferred provincial funding for diagnostic medical laboratory services to RHAs along with the mandate for the provision of these services.

Currently, RHAs receive public funding for diagnostic medical laboratory services under the population-based global funding formula. Under the authority of the Regional Health Authority Act, RHAs are responsible for allocating and managing their resources in accordance with the service priorities they establish. All RHAs contract with private providers such as DKML or MDS Kasper Laboratories for the provision of diagnostic laboratory services under various organizational structure and accountability models.

The Alberta College of Physicians and Surgeons is responsible for regulating diagnostic and treatment facilities in Alberta, including diagnostic medical laboratories under the authority of the Medical Profession Act. The College accredits, sets and enforces standards governing the operation of all facilities approved under the Hospitals Act. An Advisory Committee on Laboratory Accreditation and Quality Control advises the College on all matters pertaining to diagnostic medical laboratories.

As mentioned previously, Health Canada has approved the use of both the ELISA and Rapid fFN for TLI™ system manufactured by Adeza Biomedical Corporation as an aid in assessing the risk of pre-term delivery in <7 or <14 days from the time of sample collection in pregnant women with signs and symptoms of early PTL. The U.S. FDA has also cleared these systems for use as an aid in assessing the risk of pre-term delivery.

In summary, no provincial legislative or policy barriers are identified with respect to the introduction of fFN testing, nor would such introduction imply the need for any changes to current provincial legislation or policy.

Fit With Current Directions and Principles of Alberta’s Health System

The Alberta Health and Wellness Business Plan 2005-08 (April 13, 2005) recognizes the importance of health system innovation as one of this Ministry’s strategic priorities and mentions the importance of managing the introduction of new health care technologies. While the management of PTL is not specifically mentioned, if cost-effective, the introduction of fFN would be consistent with Goal 6: Health system efficiency, effectiveness and innovation, under AHW’s Core Business Three: Lead and participate in continuous improvement in the health system.

Introduction of fFN testing poses no potential conflict with federal or provincial health system principles.
Other Canadian Jurisdictions

The first fFN unit was installed in Regina, Saskatchewan in September 2001. Since then, pilot projects have been documented in British Columbia, Manitoba, Nova Scotia, Nunavut and Quebec. There are approximately 80 of the latest test units in Canada with two to five units being added monthly. Results of studies conducted by various hospitals or RHAs have been reported at annual meetings of the SOGC from 2003 through 2005.

A survey of all other Canadian jurisdictions as well as communication with the product’s manufacturer confirms that the performance of the rapid fFN assay is not reimbursed anywhere in Canada for diagnosing suspected pre-term labour or predicting pre-term delivery in symptomatic women.

No province has yet implemented a provincial policy that would see a province-wide system or routine application of fFN testing, although there is some indication that several jurisdictions are moving towards province-wide access to this test. The Specialized Services Committee of British Columbia’s Reproductive Care Program is currently preparing a business case for fFN testing for submission to the B.C. government and/or B.C.’s RHAs.10 A representative from Nunavut reports the completion of a pilot project involving four small health centres in the Baffin Region and, based on the findings of this pilot notes plans for expanding the use of the test to more communities.11

If implemented provincially in the near future in Alberta, this province would be the first Canadian jurisdiction to do so, although others may be close behind.

Potential Effect of Decision

Manufacturers/suppliers

The Rapid fFN for TLi™ system is manufactured by Adeza Biomedical Corporation of Sunnyvale, California and is the only supplier of this test at present. This company would stand to gain financially from the province-wide introduction of fFN testing in Alberta. Because fFN is a new test and would not be replacing comparable existing technology, no other manufacturer is likely to be affected by Alberta’s decision.

The possibility of a volume purchase could be explored with the manufacturer.

Health care providers

Introduction of this technology will affect physicians with an obstetrical practice, laboratory personnel and health care administrators.

The literature suggests the need for establishing clear protocols for the use of fFN test results in managing PTL. Initial and ongoing physician education and regular audit is necessary to ensure that potential cost-savings for fFN testing are realized. Physicians will need to change their current practice of care based on fFN results. If they provide unnecessary interventions (for example, antibiotic or tocolytic medications, hospital admission) with patients having a negative test result and increase interventions for those with a positive test result, then there is a risk that health care resources will increase rather than decrease with the use of the test.

10 Personal communication, October 21, 2005.
11 Personal correspondence, October 10, 2005.
If fFN testing is implemented, RHAs medical and administrative staff will need to work with their laboratory personnel regarding the decision of whether to place the fFN unit in a hospital laboratory or at the bedside and determine processes for specimen collection, transportation, and timely reporting of results. Availability of 24/7 access to laboratory services is critical for timely reporting and patient care decision-making.

**Patients and families**

The social and economic impact on women and their families was not specifically assessed in the studies reviewed as part of this initiative. However, one can predict a potential avoidance of negative psycho-social and financial impact annually on a number of women with false PTL as well as to their families, and employers.

If introduced with strict practice guidelines, fFN testing has the potential to limit the amount of unnecessary medical care received by women with symptoms of PTL who do not go on to preterm delivery. In addition to the possibility of unnecessary medications, current practice routinely encourages work leave and prescribes bed rest to prevent preterm birth. The normal home and work lives of women are disrupted while undergoing care. If women do not live within easy access to outpatient services, they may be hospitalized. Each year a small number of women undergo unnecessary ambulance transfers to health care centres outside of their community. A family may incur caregiver costs associated with the woman’s absence from her home during her hospitalization stay.

Conversely, the potential exists for approximately one percent of women to be inaccurately diagnosed to be in false labour. Not transferring these women based on a false negative test result may have serious implications for both the mother and preterm baby. Also, because the positive predictive value of the test is relatively low, there is a possibility for more unnecessary medical interventions and transfers for women inaccurately diagnosed with a positive test result.

**Others**

If fFN testing is implemented province-wide, standard provincial practice guidelines may be needed to ensure optimal practice and the realization of the cost savings potential. The Alberta Perinatal Health Program, Alberta College of Physicians and Surgeons and/or the Towards Optimized Practice program may be best positioned to assist in the development of such guidelines with physicians and laboratory personnel.

**Potential for Transfer of Service and Funds**

When the economic analysis is considered on a regional basis, one can predict that the greatest cost avoidance would be realized in the Calgary and Capital health regions. The costs of fFN testing should be more than offset by the savings associated with reduced LOS. One could argue that no transfer of funding or additional funding is warranted for these regions, although they may wish to consider internal budget reallocations.

The economic analysis suggests that the introduction of fFN testing in the seven non-metro regions may not result in a net savings for each region, primarily due to the equipment costs for the test units that would need to be purchased for each hospital with less than 1000 births per year. If fFN testing were to be introduced in these regions for reasons other than purely financial considerations, then one might argue that these regions would require additional funding. The costs they would be asked to bear to achieve savings in the tertiary
centres and to Alberta Health and Wellness through reduced length of stay and ambulance transfers avoided should not be borne solely by these regions.

**Summary and Policy Options**

**The Three Screens**

In this section, the results of the analysis are presented according to the three screens recommended by the Expert Advisory Panel to Review Publicly Funded Health Services.

<table>
<thead>
<tr>
<th>Screen Question</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td></td>
</tr>
<tr>
<td>Is the technology safe?</td>
<td>There is little risk to the mother or infant by performing the procedure itself. The risk is comparable to that of other routine procedures, for example, a Pap smear test. There may be harm to those patients who are inaccurately diagnosed with a negative result - that is, for the approximately one percent of women with a negative result who do go on to deliver prematurely within the two weeks (14 days) following the fFN specimen collection. Similarly, there is potential psychological and physical harm to women falsely diagnosed with a positive result resulting from receiving unnecessary interventions.</td>
</tr>
<tr>
<td>Is the technology effective?</td>
<td>The evidence supports that the negative predictive value of the fFN does aid in ruling out unnecessary interventions and preventive therapy for symptomatic women before 34 and 37 weeks of gestation. Conclusions from the most recent and comprehensive systematic review suggest that the “cervicovaginal fetal fibronectin test is most accurate in predicting spontaneous preterm birth within 7-10 days of testing among women with symptoms of threatened preterm birth before advanced cervical dilation”. It is noted that the studies reviewed were observational studies rather than RCTs and contained design flaws.</td>
</tr>
<tr>
<td>Is the technology cost-effective?</td>
<td>The literature suggests that fFN has a potential to reduce health care utilization and unnecessary treatment by more accurately identifying women who are not in true labour. However, the results are from observational studies and, for the most part, have not been confirmed in experimental RCT studies. In order for the potential to be realized, physicians must change their practice patterns when rapid fFN assay results are negative. If they continue current patterns of care when results are negative and increase interventions when results are positive, resource use may actually increase.</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Screen Question</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the technology important for redistribution?</td>
<td>The introduction of fFN would not result in significant redistribution within the health system.</td>
</tr>
<tr>
<td>What is the impact on specific populations?</td>
<td>The introduction of fFN has the potential for avoidance of negative financial, psycho-social and physical effects on women with symptoms of PTL who are not at risk for premature delivery within 14 days, through the avoidance of unnecessary health care (hospitalization and medication administration) and ambulance transfer. Their family members and employers may also be impacted.</td>
</tr>
<tr>
<td>Do other service options exist?</td>
<td>The literature suggests that fFN is superior to current practices in predicting PTL. Alternatives to fFN testing are emerging; however, these have not yet been subject to rigorous study for their effectiveness.</td>
</tr>
<tr>
<td>Do other payment options exist?</td>
<td>No.</td>
</tr>
<tr>
<td>Is there alignment with regulatory and policy frameworks?</td>
<td>Yes. The introduction of the rapid fFN testing would be consistent with Alberta's legislative and policy framework.</td>
</tr>
</tbody>
</table>

**Fiscal**

<table>
<thead>
<tr>
<th>Screen Question</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the technology affordable within the current budget?</td>
<td>Yes, there is a potential net savings to the provincial health system if fFN were introduced. This net cost savings is greatest if the test is introduced only in Level 2 and 3 hospitals.</td>
</tr>
<tr>
<td>Is it affordable with the elimination of existing, less cost-effective treatment?</td>
<td>Because fFN testing is a new technology, it would not be replacing existing technology.</td>
</tr>
<tr>
<td>Is it affordable only with new funding or revenue?</td>
<td>If a decision is made to introduce fFN into Level 1 hospitals as well as Level 2 and 3 hospitals, new funding would be needed for regions having predominantly Level 1 hospitals.</td>
</tr>
</tbody>
</table>
## Policy Options

Four policy options are identified. They are presented below, along with the main rationale for or against their adoption.

<table>
<thead>
<tr>
<th>Policy Option</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| **Option 1: Do not provide fFN testing in Alberta** | **For:** While the potential for cost savings exist, cost savings of fFN testing have not been conclusively demonstrated through strong, well-designed studies.  
• If introduced without clear clinical protocols and monitoring, there is a risk that introduction may result in increased resource utilization.  
**Against:** Results from studies conducted by the Calgary and the Capital health Regions as well as the cost analysis conducted as part of this review demonstrate a potential for net savings to the health system.  
• The test has already been introduced in the Calgary Health Region, and it would be difficult to discontinue the test in that region. |
| **Option 2: Provide fFN testing in Level 2 and 3 hospitals only.** | **For:** A cost analysis suggests the introduction of fFN testing could result in the greatest net savings to the health system if introduced in Level 2 and 3 hospitals with clear clinical guidelines, physician education and auditing.  
**Against:** This option would result in inconsistent local access to fFN testing for women.  
• A small number of women would continue to receive unnecessary transfers and suffer the inconvenience and financial burden associated with these transfers. |
| **Option 3: Provide fFN testing in all Level 1, 2 and 3 hospitals** | **For:** When compared with Option 2, women in Alberta would have more equitable access to fFN testing. There would not be a disproportionate risk for unnecessary medical care and ambulance transfer depending on where they reside in Alberta.  
**Against:** This option results in a significantly reduced net savings to the provincial health system.  
• The cost of introducing the test into health regions with predominantly Level 1 hospitals would not be |
### Fetal Fibronectin (fFN): Synthesis Report

<table>
<thead>
<tr>
<th>Policy Option</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>annual variable costs would be $147,850.</td>
<td>offset within those regions by savings associated with reduced LOS and avoidance of ambulance transfers. New funding would be needed for these regions.</td>
</tr>
<tr>
<td>These costs would be offset, primarily through reductions in length of hospital stay.</td>
<td></td>
</tr>
</tbody>
</table>

**Option 4: Provide fFN testing in all Level 2 and 3 hospitals and in selected Level 1 hospitals based on their proximity to Level 2 or 3 hospitals and number of births per year.**

A sample scenario may involve Level 1 hospitals that:
- are located 1 hour or more from a Level 2 or 3 hospital, and
- have more than 100 births/year.

About 23 Level 1 hospitals currently meet these sample criteria. In total, about 33 hospitals located in nine regions would provide fFN testing.

The one-time fixed cost for this example is estimated at $64,032. The annual variable costs are estimated to be $138,901.

More investigation would need to occur to determine the optimal criteria for determining which Level 1 hospitals would receive the fFN units under this scenario.

**For:**
- This alternative is a compromise between options 2 and 3. It strategically targets those areas of the province where ambulance and family costs may be the greatest (i.e., those located farthest from Level 2 or 3 hospitals) and those hospitals that, because of birth volume, may generate the most ambulance transfers among Level 1 hospitals.

**Against:**
- A small number of women would continue to receive unnecessary transfers and suffer the inconvenience and financial burden associated with these transfers, although this number would be minimized.
Appendix A:

List of Analysis Reports


Appendix B:

Fetal Fibronectin (fFN) Expert Advisory Group

- Henry Borowski, Director, Health Technologies and Services Policy, AHW (Committee Chair)
- Joan Berezanski, Director, Provincial Medical Care Consultant’s Office, AHW
- Dr. Gail Black, Physician, Capital Health, Obstetrician (urban)
- Dr. Michael Caffaro, Physician, Aspen Regional Health Authority, Family physician (rural)
- Dr. Raymond Howard, Medical Consultant, AHW, Project Medical Consultant
- Selikke Janes-Kelley, Patient Care Director, Women’s Health, Royal Alex. Hospital, (Urban RHA – accepting centre)
- Dr. Ian Lange, Dept Head, Obstetrics & Gynecology, Calgary Health Region, Alberta Perinatal Health Program
- Nell Vrolyk, Vice-President, Health Services, Northern Lights Health Region, Rural RHA – remote transporting centre

Fetal Fibronectin (fFN) Project Team

- Henry Borowski, Director, Health Technologies and Services Policy, AHW
- Paula Corabian, Alberta Heritage Foundation for Medical Research, (Technological Effects/Effectiveness)
- Dr. Gillian Currie, University of Calgary, Institute of Health Economics, (Economic Evaluation, Social/System Demographics)
- Dr. Habib Fatoo, Health Economics, Health Funding and Costing, AHW
- Christa Harstall, Alberta Heritage Foundation for Medical Research, (Technological Effects/Effectiveness)
- Dr. Raymond Howard, Medical Consultant, AHW, Project Medical Consultant
- Kasia Kunikiewicz, Health Economics, Health Funding and Costing, AHW
- Brenda Petzold, Project Manager, Health Technologies and Services Policy, AHW