Measurement of Total Bile Acids
(Reference – 2013.03.001)
Notice of Assessment

April 2014
1 GENERAL INFORMATION

1.1 Requestors: CHU Sainte-Justine; Hôpital Saint-Luc (CHUM)

1.2 Application for Review Submitted to MSSS
- CHU Sainte-Justine: June 15, 2013

1.3 Application Received by INESSS: November 1, 2013

1.4 Notice Issued: February 28, 2014

Note:
This notice is based on the scientific and commercial information submitted by the requestor and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology
Measurement of total serum bile acids (salts) in pregnant women to establish cholestasis of pregnancy as a diagnosis of exclusion. This quantitative assay is carried out using an enzymatic method and measured by absorbance at 410 nm on a Beckman-Coulter (HSJ) or Cobas (HSL) analyzer.

2.2 Brief Description of the Technology, and Clinical and Technical Specifications
Bile acids are the end products of cholesterol catabolism [Egan et al., 2012; Walker et al., 2002]. More than 90% of bile acid synthesis occurs in hepatocytes, while the remainder occurs extrahepatically [Egan et al., 2012].

Bile acids in humans share an alpha-hydroxyl radical in position 3, which endows them with detergent properties that allow the digestion and absorption of fatty acids and lipids by the intestinal villi. The primary bile acids synthesized by the liver are cholic acid (CA) and chenodeoxycholic acid (CDCA). Secondary bile acids, deoxycholic acid (DCA) and lithocholic acids (LCA), are the products of bacterial modification, deconjugation, and 7-alpha-dehydroxylation, which alters their structure in the terminal ileum and colon (Figure 1).
Ursodeoxycholic acid (UDCA), a tertiary bile acid detectable in humans in trace amounts, is the product of bacterial modifications in the digestive tract and hepatic metabolism [Walker et al., 2002].

The secretion of bile acids across the canalicular membrane of hepatocytes is coordinated by various energy-consuming (mainly ATP dependent) and self-regulated transport mechanisms. These self-regulating canalicular transport mechanisms are the most likely cause of the various manifestations of intrahepatic cholestasis.
Thus, 30 g of bile acids are secreted by the liver (initially from 0.5 g of cholesterol) every day. The bile is stored in the gallbladder and released into the lumen of the duodenum when food is ingested. The bile is then reabsorbed in the terminal ileum and returned to the liver via the portal vein (enterohepatic circulation). Approximately 5% of bile acids are lost through the feces.

When a meal is consumed, 4 to 6 g of bile are secreted, for a total of 12 g to 18 g or up to 30 g of bile salts each day. Consequently, the reabsorption cycle may be reactivated 3 to 15 times a day, as needed [Walker et al., 2002].

The concentration of bile salts increases from 20 mmol/L to 50 mmol/L in the bile canaliculi and may reach 300 mmol/L in the gallbladder; it ranges from 20 µmol/L to 50 µmol/L in the portal vein and from 3 µmol/L to 5 µmol/L in peripheral blood during fasting [Walker et al., 2002]. After a meal, this concentration increases from 2 to 5 times and reaches peak values 60 min to 90 min after the meal. These changes are less significant with high pathological levels [Walker et al., 2002].

Various methods may be used to measure blood levels of bile salts. They can be measured separately using sophisticated analytical methods such as high-performance liquid chromatography (HPLC), gas chromatography coupled with mass spectrometry (GC-MS) or other MS (such as FAB-MS\(^1\)), or tandem GC-MS techniques [Dias, 2012; Ducroq et al., 2010; Rani et al., 2006; Walker et al., 2002; Azer et al., 1997; Bacq et al., 1995]. Total bile acids can easily be quantified with conventional enzymatic spectrophotometric methods, based on their common biochemical structure, using the 3-alpha-hydroxysteroid dehydrogenase (3α-HSD) enzyme. Various commercial kits can perform this measurement with an autoanalyzer and optical scanner. Fifth-generation enzyme assays are the most commonly used (Figure 2).

**Figure 2: Current enzymatic methods Designed to measure bile acids**

![Diagram of enzymatic methods](image)

Source: Ducroq et al., 2010. Figure reproduced with permission of the author.

### 2.3 Company or Developer

The two recommended kits use the same quantitative enzyme assay methodology.

Hôpital Saint-Luc (CHUM): BQ Kits. Quantitative determination of total serum bile acids (enzymatic cycling) fifth generation (Catalog No. BQ 042A-EALD-USA):

- using 3-alpha-HSD;
- Cobas 311 analyzer;
- absorbance: 405 nm.

Note: Randox internal quality control and RCPAQAP (Australia) external quality control are used.

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\(^1\) FAB-MS: fast atom bombardment-mass spectrometry.
CHU Sainte-Justine: Randox Kit – fifth generation enzymatic-colorimetric assay (Catalog No. BI 3863-Ireland):
- using 3-alpha-HSD;
- Beckman Coulter DxC 880i analyzer;
- absorbance: 410 nm.

2.4 Licence(s): Not applicable.
2.5 Patent, If Any: Not applicable.
2.6 Approval Status (Health Canada, FDA)
FDA: For research purposes only.
BQ: Not registered for use in Canada. The company is planning to submit an application for approval in Canada (according to CHUM’s requestor, personal communication, December 2013).
Randox: Although the requestor has indicated that the kit is registered in Canada, this could not be confirmed. In fact, the only enzymatic total bile acids assay kit approved in Canada appears to be a product registered in 2007 by Diazyme Laboratories in California (Health Canada 74467).

2.7 Weighted Value
- Hôpital Saint-Luc (CHUM) (BQ Kits): 19.87
- CHU Sainte-Justine (Randox Kit): 43.22
The considerable difference between the two requestors’ weighted values is due to the number of internal controls (3) performed for each sample assayed at the CHU Sainte-Justine; hence, the mean difference in values between the two requestors’ laboratories stems from the reagents and materials and amounts to $10.87/patient at the CHUM Saint-Luc and $34.87/patient at the CHU Sainte-Justine.

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patient Group
Pregnant women experiencing pruritus during the second half of their pregnancy, without any skin lesions other than those caused by scratching. Pruritus is continuous and generalized, although it is more pronounced in the palms of the hands and soles of the feet [Pata et al., 2011], and resolves within 4 to 21 days after delivery [Pusl and Beuers, 2007]. Cholestasis of pregnancy is a diagnosis of exclusion if there are no signs of biliary or hepatic obstruction, infectious or toxic hepatitis, fever or other pruriginous systemic diseases (i.e., Hodgkin disease) [Gaudet et al., 2000]. Preeclampsia, HELLP (hemolysis, liver enzymes, low platelets) syndrome, and acute fatty liver of pregnancy also are very serious obstetric differential diagnoses to consider.

The quantitative determination of total bile acids, among other relevant liver function tests, allows the diagnosis of intrahepatic cholestasis to be confirmed or ruled out [Chen et al., 2013; Egan et al., 2012; RCOG, 2011; Wong et al., 2008; Walker et al., 2002].

3.2 Targeted Disease(s)
Cholestasis of pregnancy (intrahepatic cholestasis of pregnancy) usually develops after 30 weeks’ gestation [Pusl and Beuers, 2007], although it can occur earlier (as early as 8 weeks’ gestation) [Geenes and Williamson, 2009], particularly in the case of a multiple pregnancy [Pusl and Beuers, 2007].
The etiology of the disorder has not been fully established; certain hormonal factors have been noted, such as the high concentration of estrogens during pregnancy (particularly multiple pregnancies) and
its recurrence (45% to 75%) in subsequent pregnancies or with the use of oral contraceptives. It has also been suggested that hormones might have an effect in genetically susceptible women [Geenes and Williamson, 2009]. Certain candidate genes have been identified [Diken et al., 2014], and a 12-fold increased risk was observed in sisters of affected patients [Müllenbach et al., 2005]. Genetic influence could, in part, account for the variations in the prevalence of this condition in different ethnic groups and countries. Its prevalence is less than 1% in Asia, Australia, and North America [Pusl and Beuers, 2007] and ranges from 0.2% to 0.5% in France [Gaudet et al., 2000]. It is 10.2% in Scandinavian countries and Portugal [Pata et al., 2011; Glantz et al., 2004] and approximately 10% in South American countries such as Bolivia and Chile [Gaudet et al., 2000]. The highest prevalence was reported in certain indigenous populations of South America: 13.8% among the Aymara of Bolivia and 27.6% among the Araucanians of Chile [Geenes and Williamson, 2009; Pusl and Beuers, 2007].

At exceedingly high concentrations, bile acids are toxic. In fact, high intracellular levels are associated with oxidative damage and apoptosis in adult and fetal liver [Egan et al., 2012] and may lead to carcinogenesis in adults [Debruyne et al., 2001].

The effect on the mother is primarily that of intense pruritus associated with reduced quality of life caused by lack of sleep, which in some cases may be so severe as to necessitate premature delivery when symptomatic and specific treatments (UDCA) are not effective. Some studies reported a higher incidence of postpartum hemorrhage, but this was not confirmed in all the publications [Walker et al., 2002].

Furthermore, an increase in serum bile acids increases myometrial sensitivity to oxytocin and prostaglandin secretion, which explains the occurrence of spontaneous preterm births (19.6% and 32.5%, respectively) [Pusl and Beuers, 2007; Gaudet et al., 2000].

An increase in bile acid levels may be particularly harmful to the fetus. Bile salts can easily cross the placental barrier, leading to a dangerous build-up of bile acids in the fetus, in which metabolic immaturity prevents detoxification [Gaudet et al., 2000]. In utero deaths have been reported (0.4% to 4.1%), particularly when total bile acid levels exceeded 40 µmol/L [Pusl and Beuers, 2007]. Growth delay is common (18.8%) [Gaudet et al., 2000], as are abnormal fetal heart rate patterns (15%) and fetal distress during delivery (22% to 41%) [Wong et al., 2008; Pusl and Beuers, 2007]. Taking all morbidities into account, Gaudet et al. [2000] estimated the risk of fetal complications from cholestasis to be 59%.

According to a recent literature review [Diken et al., 2014], the rates of perinatal morbidity range from 3.5% to 11%, of preterm delivery from 36% to 38%, of meconium-stained amniotic fluid from 27% to 45%, and of intrapartum fetal distress from 14% to 22%. There appears to be a direct relationship between the circulating concentration of bile acids and fetal and neonatal complications. Some studies report a concentration greater than 40 µmol/L [Glantz et al., 2004], whereas others report a threshold greater than 100 µmol/L [Diken et al., 2014]. A meta-analysis of randomized clinical trials showed the protective effect of UDCA on the fetus, with a reduction in the rates of preterm births, fetal distress, respiratory distress syndrome, and admissions to neonatal intensive care, but not in utero mortality rates [Bacq et al., 2012].

Therefore, it is important to quickly establish a diagnosis in order to determine the most appropriate treatment.

3.3 Number of Patients Targeted

Given its prevalence of < 1.0%, approximately 900 cases of cholestasis of pregnancy are expected each year in Quebec, and a higher prevalence (5- to 12-fold, according to the authors) is expected in multiple pregnancies and among pregnant women from Scandinavian countries and especially from South
America (Chile and Bolivia). It should be noted that the incidence of cholestasis of pregnancy shows seasonal variations; it generally occurs in the winter and early spring.

3.4 Medical Specialties and Other Professions Involved

All health care professionals involved in prenatal care, as well as biochemists in laboratories, to ensure quality control and to allow the clinical professionals concerned to obtain results promptly.

3.5 Testing Procedure

After diagnosis, quantitative assays should be performed regularly to assess the severity of the condition or its improvement after specific treatment with UDCA. In 9 randomized controlled trials [Bacq et al., 2012], the assays were repeated every 2 to 3 weeks after the initial assay and the beginning of treatment.

It is recommended that a fasting blood sample be taken (although there will be little variation during fasting if the concentration is already very high) for the enzyme test.

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology

This test is not listed in the Index and is performed outside Quebec.

From 2012 to 2013, 211 tests were performed in Toronto (Hospitals In-Common Laboratory Inc., unit cost $17.00), in Hamilton, Ontario (Hamilton General Hospital, unit cost $11.00 or $14.00) and in Cincinnati (Cincinnati Children’s Hospital Medical Center, unit cost $843.00 to $930.00).

4.2 Brief Description of the Current Technological Context

The current technology uses a fifth generation enzymatic method (see 2.2) that has the advantage of measuring all bile acids, free and conjugated, with an automated technique that produces a reading in less than a minute.

This technique is now recognized as being the simplest, most rapid, and most cost-effective [Bailey et al., 2012; Dias, 2012; Rani et al., 2006; Azer et al., 1997].

Total bile acid assays measure serum concentrations of free or conjugated primary bile acids (cholic acid: CA; chenodeoxycholic acid: CDCA), secondary bile acids (deoxycholic acid: DCA; lithocholic acid: LCA), and tertiary bile acids (ursodeoxycholic acid: UDCA).

Figure 3 shows the concentration of each of these compounds in non-pregnant women, women with normal pregnancies in the third trimester, and women with cholestatic pregnancies. It may be noted that, on average, the total concentration of bile acids is $5.7 \pm 0.4 \mu mol/L$ in non-pregnant women (in this case, a Caucasian Portuguese population), and slightly higher, although not significantly, in the pregnant group ($6.6 \pm 0.3 \mu mol/L$, ranging from $1.7 \mu mol/L$ to $10.4 \mu mol/L$). However, in the Portuguese women with cholestasis of pregnancy, the mean concentration was 10 times higher at $62.1 \pm 8.2 \mu mol/L$, ranging from $12.3 \mu mol/L$ to $219.4 \mu mol/L$ [Brites et al., 1998].
Figure 3: Mean concentrations of the various free or conjugated bile acids in non-pregnant women and pregnant women with or without cholestasis of pregnancy

It should be noted that the proportions of the various bile acids are similar in pregnant and non-pregnant women, whereas cholic acid is higher in women with cholestasis of pregnancy, [Brites et al., 1998; Figure 4].

Figure 4: Relative proportions of the various bile acids in non-pregnant women, pregnant women, and women with cholestatic pregnancies

Another team [Egan et al., 2012] conducted a cross-sectional study to assess circulating bile acid levels during pregnancy in just over 200 Caucasian Irish women with a normal singleton pregnancy. The samples, taken at 12, 20, 28, and 36 weeks of gestation and in the immediate postpartum period, showed similar concentrations during pregnancy, with a median ranging from 2.9 µmol/L to 3.5 µmol/L, and in the postpartum period (median 2.6 µmol/L). More than 98% of the values were less than 10 µmol/L, with values in 216 of the 219 women ranging from 0.3 µmol/L to 9.8 µmol/L, the other three measurements being 16.7 µmol/L, 12.0 µmol/L, and 11.6 µmol/L, which allowed a maximum threshold value of 10 µmol/L to be established for pregnant women [Egan et al., 2012]. Most authors
[Diken et al., 2014; Geenes and Williamson, 2009; Wong et al., 2008; Pusl and Beuers, 2007; Gaudet et al., 2000] agree on a threshold value of 6 µmol/L to 14 µmol/L.

4.3 Brief Description of the Advantages Cited for the New Technology

The enzymatic method is not only easy to perform with an analyzer, but also simple, easily accessible, rapid, and inexpensive. A key advantage of this laboratory test is that it can be performed in Quebec; consequently, the results can be obtained very quickly, allowing prompt confirmation of the diagnosis, administration of specific treatment, monitoring of the treatment’s progress, and, potentially, prevention of excess perinatal mortality and morbidity.

4.4 Cost of Technology and Options: Not assessed.

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced

The new test being introduced is currently performed outside Quebec.

5.1.2 Diagnostic or Prognostic Value

In pregnant women experiencing pruritus during the second half of their pregnancy, a diagnosis of cholestasis of pregnancy is established by abnormally high concentrations of bile acids in the blood (> 10 µmol/L), while the results of the other liver function tests are normal, at the upper limit of normal, or slightly higher during the pregnancy. Bilirubin levels may be slightly elevated [Chen et al., 2013; Diken et al., 2014; RCOG, 2011; Brites et al., 1998]. It should be noted that pruritus is relatively common during pregnancy (approximately 1 in 4 women) and that it is caused by cholestasis of pregnancy in only a small proportion (≤ 1%) of cases [RCOG, 2011].

Severe cholestasis of pregnancy occurs when serum levels reach 40 µmol/L or 100 µmol/L; there is a major risk of perinatal mortality and morbidity starting at 40 µmol/L [Chen et al., 2013; Pata et al., 2011; RCOG, 2011; Glantz et al., 2004].

Specific maternal treatment has proved to be effective in improving fetal prognosis [Bacq et al., 2012]. Performing the assays at weeks 1, 2, and 3 (according to the authors), after treatment was administered, allows the response to treatment and any improvement in the condition to be assessed [Bacq et al., 2012; RCOG, 2011]. In the case of nonresponse, preterm labour induction must be considered to prevent perinatal complications and relieve the mother’s severe pruritus.

5.1.3 Therapeutic Value

The therapeutic options are to continue the pregnancy, which is preferable when the condition has improved or serum bile acids concentrations have decreased, or to induce preterm birth, if the condition has not improved.
## 5.2 Clinical Validity

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<tr>
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<td>Accuracy</td>
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The sensitivity needed to detect the disease with bile acids depends on the established threshold level, which can range from 6 µmol/L to 14 µmol/L, depending on the publication referenced. In Ireland, Wong et al. [2008] confirmed a diagnosis of cholestasis of pregnancy at a level of 6 µmol/L for 151 of the 769 pregnancies with pruritus, a prevalence of 20% of such pregnancies, but only 0.84% of all pregnancies observed. However, premature deliveries occurred only at a total bile acids level of ≥ 11 µmol/L.

At a threshold level of ≥ 11 µmol/L, Brites et al. [1998] obtained a sensitivity of 100% and a specificity of 89%. In Sweden, Glantz et al. [2004] observed 505 pregnancies with bile acid levels ≥ 10 µmol/L, or 1.5% of the 45,485 pregnancies that occurred during the study period. Among the cases of cholestasis of pregnancy, 81% (n = 409) were considered mild (bile acid levels from 10 µmol/L to 39 µmol/L) and 19% (n = 96) severe (bile acid levels ≥ 40 µmol/L). Surprisingly, no fetal complications were observed in the group with mild cases of cholestasis; it was only when concentrations were as high as 40 µmol/L that premature births and cases of perinatal asphyxia occurred.

Nevertheless, bile salt assays are the most sensitive and specific means of detecting cholestasis of pregnancy in the presence of pruritus [Geenes and Williamson, 2009; Walker et al., 2002], compared with all other liver function tests, which may or may not show abnormal results. Moreover, in some cases, bile salt levels may rise before other liver function tests show abnormal results [Walker et al., 2002].

Only one publication reported a false-positive rate of 7.5% and false-negative rate of 10.0%, for a threshold total bile acid level of 33.6 µmol/L, when measured using HPLC-MS [Chen et al., 2013].

## 5.3 Analytical (or Technical) Validity

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<td>Analytical sensitivity</td>
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The analytical validity presented concerns the enzymatic method (fifth generation) of the two kits (Randox, BQ Kits) used by the two requestors. If necessary, this method will be compared with other methods.
Measurement error, either in the measurements repeated during a test (intra-assay variability) or during various tests (inter-assay variability), is expressed as a coefficient of variation for a given concentration. This variation is minimal and ranges from 0% to 4.5% (intra-assay) and from 0.9% to 4.14% (inter-assay) for total bile salt concentrations of 5 µmol/L to 95 µmol/L (Appendix A). Dr. Marie-Claire Bélanger, of the CHUM, validated the measurement error in her laboratory. In addition, she took part in an Australian external quality assurance program (RCPAQAP), during which 10 samples of 6 µmol/L to 79 µmol/L were assessed, yielding a correlation coefficient of \( r^2 = 0.9992 \) (personal communication, December 17, 2013).

Analytical sensitivity is excellent and includes free and conjugated forms of total bile acids, due to their biochemical structure.

Analytical specificity, that is, the capacity to differentiate between bile salts and interferences in the enzymatic method used, also is excellent. The Randox kit shows an interference of less that 10% from triglycerides, ascorbic acid, bilirubin, and hemoglobin.

Concordance, or the measurement obtained with the enzymatic method compared with that obtained with another reference method, was reported from a comparison with the measurement obtained with HPLC: the resulting measurements had a mean of 43.4 µmol/L ± 24.0 µmol/L with the enzymatic method, versus 43.5 µmol/L ± 22.6 µmol/L with HPLC (\( r^2 = 0.97 \)) [Bacq et al., 1995]. When the fifth generation enzymatic method (Thio-NADH) was compared with the third generation method (Formozan), the correlation coefficients from three comparisons conducted were excellent (\( r^2 = 0.9696 \) : CHUM; 0.99: Randox kit; 0.94 from 174 samples; Dias et al., 2012).

The linearity of the measurements was excellent, between 0 µmol/L and 150 µmol/L or 180 µmol/L, depending on the kits proposed (Randox, BQ Kits). Bailey et al. [2012] reported \( r^2 = 0.9991 \) between 2 µmol/L and 105 µmol/L.

Recovery with a serial dilution showed a correlation ranging from 93% to 123% for concentrations of 1 µmol/L to 170 µmol/L [Dias et al., 2012], whereas Bailey et al. [2012] reported a mean of 106% or 95% for fifth or third generation methods at concentrations of 10 µmol/L to 100 µmol/L of the main bile acid, taurocholic acid.

The minimum detectable concentration, other than zero, ranges from 0.2 µmol/L to 0.4 µmol/L for fifth and third generation kits, respectively [Bailey et al., 2012].

The stability of the reagents is ensured for 7 days (−2°C to −8°C), according to manufacturers (Randox, BQ Kits), but it is reported to be 30 days by Bailey et al. [2012] and 3 months at −20°C (Randox, BQ Kits).

### 5.4 Recommendations from Other Organizations

In Ontario, the test is used primarily for the diagnosis of cholestasis of pregnancy and certain rare pediatric conditions.

In the United Kingdom, the Royal College of Obstetricians and Gynaecologists recommends the measurement of total bile acids to establish a definitive diagnosis of cholestasis of pregnancy and to follow its progression [RCOG, 2011].

A follow-up is recommended every 7 to 14 days after the diagnosis has been made. Obstetrics manuals are in agreement with this recommendation.
6 ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources
Although this test is performed outside Quebec, an increase in the number of assays is expected. However, the test is simple and easy to perform, and the absorbance reading is taken with an analyzer. The test is also inexpensive; Bailey et al. [2012] reported a reagent cost of $5.97 with BQ Kits in Ontario. It should be noted that the number of requests is expected to increase, particularly in winter and early spring.

6.2 Economic Consequences of Introducing Test Into Quebec’s Health Care and Social Services System: Not available.

6.3 Main Organizational, Ethical, and Other (Social, Legal, Political) Issues
This test should be available in high-risk pregnancy centres, where cholestasis of pregnancy should be managed, due to the perinatal mortality and morbidity rates reported.

7 IN BRIEF

7.1 Clinical Relevance
The measurement of total bile acids is essential in making a diagnosis of cholestasis of pregnancy, which affects approximately 1% of pregnant women, particularly towards the 30th week of pregnancy. It can be used for the differential diagnosis of a number of pruritic skin diseases commonly afflicting women during pregnancy, as well as systemic diseases associated with impaired hepatic function and especially very serious pregnancy-related diseases such as eclampsia, HELLP syndrome, and acute fatty liver of pregnancy.

7.2 Clinical Validity
The clinical validity is very well established. Total bile acid levels are elevated only in cholestasis of pregnancy. The sensitivity is often 100%, with a specificity of 80% to 85%. The circulating concentration is almost the same in non-pregnant and pregnant women and ranges from 0 µmol/L to less than 10 µmol/L. The pathological detection threshold is set at greater than 10 µmol/L, and some estimate that the condition is serious when the measurement is greater than 40 µmol/L or 100 µmol/L.

7.3 Analytical Validity
Quantitative enzyme assays are accurate, reliable, valid, and reproducible.

7.4 Recommendations from Other Organizations
Widely recognized and employed, and strongly recommended by the NHS and the Royal College of Obstetricians and Gynaecologists in the United Kingdom.
8  INESSS NOTICE IN BRIEF

Measurement of Total Bile Acids

<table>
<thead>
<tr>
<th>Status of the Diagnostic Technology</th>
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<td>☒ Established</td>
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<td>☐ Innovative</td>
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<td>☒ Replacement for technology: __________________________, which becomes obsolete</td>
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<tr>
<td>☐ Draw connection with listing of drugs, if companion test</td>
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<tr>
<td>☐ Produce an optimal use manual</td>
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<td>☐ Identify indicators, when monitoring is required</td>
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NOTE:

Measures must be taken to ensure internal and external quality control.

A decision algorithm with specific instructions for this test must be developed to prevent the test from being routinely performed on all pregnant women with pruritus.

It is important to ensure that response time is fast (one of the applications indicates that the analysis does not have a fast response time) and that it meets clinical needs.

Fair and rapid access to the test must be ensured on the territory because of the risks to the fetus.
REFERENCES


BQ Kits. Total bile acids assay kits (Enzymatic cycling). Catalog number: BQ042A-EALD. Performance characteristics.


## APPENDIX A
Measurement Error (Repeatability — Reproducibility)

<table>
<thead>
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<th>AUTHORS, YEAR</th>
<th>INTRA-ASSAY VARIABILITY</th>
<th>INTER-ASSAY VARIABILITY</th>
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<td>CV: %</td>
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<td>41.2 µmol/L 2.0</td>
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<td></td>
<td>91 µmol/L 0</td>
<td></td>
</tr>
<tr>
<td>CHUM (2013) – September 2012</td>
<td>16 µmol/L 4.4</td>
<td>31 µmol/L 3.6</td>
</tr>
<tr>
<td></td>
<td>91 µmol/L 3.9</td>
<td></td>
</tr>
<tr>
<td>CHUM (2013) – 8 days</td>
<td>17 µmol/L</td>
<td>32 µmol/L</td>
</tr>
<tr>
<td></td>
<td>95 µmol/L</td>
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</tr>
<tr>
<td></td>
<td>36 µmol/L (pool)</td>
<td></td>
</tr>
<tr>
<td>CHUM (2013) – 7 days (100 measurements)</td>
<td>36 µmol/L</td>
<td></td>
</tr>
<tr>
<td>CHUM (2013) – 3 months (37 measurements)</td>
<td>36 µmol/L</td>
<td></td>
</tr>
</tbody>
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