

**The ¹³C-Urea Breath Test
for Detection of *Helicobacter
pylori***

Potential Applications in Québec

AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

The ¹³C-Urea Breath Test for Detection of *Helicobacter pylori*

Potential Applications in Québec

Technology brief prepared for AETMIS
by Lonny Erickson

December 2005

The content of this publication was written and produced by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Both the original report and its French version, titled *Le test respiratoire à l'urée marquée au ¹³C pour la détection de Helicobacter pylori : possibilités d'application au Québec*, are available in PDF format on the Agency's Web site.

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How to cite this document:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). The ¹³C-Urea Breath Test for Detection of *Helicobacter pylori*: Potential Applications in Québec. Report prepared by Lonny Erickson (AETMIS 05-05). Montréal: AETMIS, 2005, ix–23 p.

Legal deposit

Bibliothèque nationale du Québec, 2005
Library and Archives Canada, 2005
ISBN 2-550-45843-5 (Printed) (French edition ISBN 2-550-45841-9)
ISBN 2-550-45844-3 (PDF) (French edition ISBN 2-550-45842-7)

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MISSION

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health-care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

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FOREWORD

THE ¹³C-UREA BREATH TEST FOR DETECTION OF *HELICOBACTER PYLORI*: POTENTIAL APPLICATIONS IN QUÉBEC

Infection with *Helicobacter pylori*, a bacterium which plays an important role in the pathogenesis of gastroduodenal disorders, is a common problem affecting 20% to 40% of Canadians. The usual clinical manifestation of this infection is dyspepsia, meaning one or more symptoms referable to the upper gastrointestinal tract. Detection of *H. pylori* infection is therefore essential to dyspepsia management.

Many methods have been developed to detect *H. pylori*. Among invasive techniques, endoscopy with biopsy is recognized as an effective method, although expensive and uncomfortable for patients. Other less invasive detection methods have been developed, notably urea breath tests. In Québec, the urea breath test using radioactive (¹⁴C) carbon is used in hospitals with nuclear medicine departments. Another urea breath test exists which is non-radioactive, using a heavy isotope of carbon (¹³C). This test was added to the list of publicly covered laboratory procedures in April 2005.

At the request of the Québec Ministry of Health and Social Services, this technology brief examines different methods for detection of *H. pylori* as well as the pertinence of increased utilization of the ¹³C-urea breath test in Québec.

Results of the literature review confirm the superiority of urea breath tests compared to other detection methods for *H. pylori* and also show that the ¹³C-urea breath test is a proven technique that is easy to administer at a reasonable cost. The fact that this test is non-radioactive allows patients suffering from dyspepsia to have access to a non-invasive diagnostic test across the province.

Therefore, AETMIS considers that the ¹³C-urea breath test should be available in all regions of Québec in health-care institutions where quality of administration can be ensured. In addition, clinicians should be informed of the availability of the test and also participate in the definition of optimal conditions of use of this test. Finally, due to the expected evolution of testing methods for *H. pylori* in the near future, this area should be periodically re-evaluated in light of new developments.

In producing this technology brief, AETMIS aims to contribute to the improvement of health of persons suffering from dyspepsia in Québec.

Dr. Luc Deschênes
President and Chief Executive Officer



ACKNOWLEDGEMENTS

This report was prepared by **Lonny Erickson**, Ph.D., consultant researcher, at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS).

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DISCLOSURE OF CONFLICT OF INTEREST

None declared.

SUMMARY

INTRODUCTION

Helicobacter pylori bacteria plays an important role in the pathogenesis of gastroduodenal disorders. This is usually observed as dyspepsia, which refers to one or more symptoms referable to the upper gastrointestinal tract. The prevalence of *H. pylori* infection in Canadians is estimated to be between 20% and 40%. This technology brief, conducted at the request of the Québec Ministry of Health and Social Services (MSSS), examines different detection methods for *H. pylori* available for patients suffering from dyspepsia as well as the relevance of increasing utilization of the ¹³C-urea breath test in Québec.

MANAGEMENT STRATEGIES FOR DYSPEPSIA

Endoscopy is the gold standard for diagnosis of *H. pylori* infection, permitting the collection of samples for biopsy to confirm infection and initiate eradication therapy when results are positive.

There is currently a great deal of interest in the non-invasive 'test and treat' strategy, which consists of non-invasive testing for *H. pylori* followed by appropriate treatment when results are positive. This strategy is recommended by recent clinical guidelines and Canadian and international consensus conferences. A second test to confirm eradication of *H. pylori* may be conducted following treatment.

NON-INVASIVE METHODS FOR DETECTION OF *H. PYLORI*

Non-invasive testing methods for detection of *H. pylori* or confirmation of eradication include: 1) antibody tests (in serum, saliva or blood); 2) antigen tests (in stools, saliva or urine); and 3) radioactive or non-radioactive urea breath tests.

Antibody detection tests are available in Québec at low cost. They have a good negative predictive value, but also have a high rate of false-positive results because antibodies persist for a long period of time after the bacteria have been eradicated. In addition, they are not appropriate to confirm eradication due to this persistence of antibodies even after active infection has been eliminated.

Many antigen tests also exist, however the test for which there is currently the most interest is the detection of antigens in stool samples by enzyme immunoassay technique. While this test has good performance at a reasonable cost, doubts exist regarding patient and clinician compliance and actual performance, particularly with regard to interlaboratory variability.

The urea breath test is based on analysis of samples of exhaled air before and after ingestion of urea containing specially labelled carbon. *H. pylori* produces an enzyme, called urease, which converts urea into carbon dioxide and ammonia. The carbon dioxide is excreted in air exhaled from the lungs, and the quantity of labelled carbon can be measured in a sample of this exhaled air to determine the presence of active *H. pylori* infection in the stomach. Carbon in the urea can be labelled with a radioactive isotope, carbon 14, or a heavy stable isotope, carbon 13. The breath test performs extremely well, regardless of the labelling method used.

COMPARISON OF RADIOACTIVE (¹⁴C) AND NON-RADIOACTIVE (¹³C) VERSIONS OF THE UREA BREATH TEST

The performance of these two tests is virtually identical, therefore practical considerations should determine the choice between either one in a given context for a particular patient.

The radioactive ^{14}C -urea breath test must be administered in hospitals with nuclear medicine departments, which restricts its accessibility. Despite the fact that the actual dose of radiation is very low, this test is contra-indicated for pregnant women and young children. In Québec, this test is publicly covered and offered in several hospitals. The total volume of tests administered in Québec is unknown, however it is known that some large hospitals in Montréal conduct over 1000 tests per year. The MSSS assigns a value of 45 technical units in the nuclear medicine department to this test (the monetary value of a technical unit varies between hospitals).

The ^{13}C -urea breath test was added to the list of publicly covered laboratory tests in Québec in April of 2005. Until recently, only private laboratories used this test. Currently, this test is not very well known in Québec. Due to the fact that this test is not radioactive, it can be widely administered in all regions of Québec. Samples can be sent for analysis to a laboratory with a mass spectrometer, which is required for analysis. The weighted value in biochemical laboratory units assigned to this test by the MSSS is equal to 40 (it is estimated that one unit equals C\$1).

Precise estimation of costs of urea breath tests in Québec is beyond the scope of this technology brief. Published Canadian studies have used values ranging from \$40 to \$120 for the ^{13}C -urea breath test. However, methods for calculation of costs vary between studies, therefore caution must be applied in the interpretation of these values.

CONCLUSIONS AND RECOMMENDATIONS

Results of the literature review confirm the superiority of urea breath tests compared to other detection methods for *H. pylori* and indicate that the ^{13}C -urea breath test is a proven technique, easy to administer, at a cost quite similar to that of the ^{14}C -urea breath test. The fact that the ^{13}C -urea breath test is not radioactive allows patients suffering from dyspepsia to have access to a non-invasive test across the province. AETMIS recommends that the ^{13}C -urea breath test be made available in all regions of Québec, and also proposes the following to ensure optimal use of this test:

- Patients in public health-care institutions in all regions should have access to the ^{13}C -urea breath test.
- Centres that administer the ^{13}C -urea breath test must respect proper procedures and ensure quality control.
- Clinicians should be informed of the availability of this test.
- Clinicians involved (gastroenterologists, pediatricians, general practitioners) should define optimal use of this test for diagnosis and confirmation of eradication of *H. pylori* in current clinical practice.
- Due to the expected evolution of various testing options for *H. pylori*, developments in all types of invasive and non-invasive testing in this area should be periodically re-evaluated in collaboration with experts in this area in Québec (members of the Canadian Helicobacter Study Group, for instance).



LIST OF ABBREVIATIONS

AETMIS	Agence d'évaluation des technologies et des modes d'intervention en santé
ASA	Acetylsalicylic acid
CHSG	Canadian Helicobacter Study Group
CHUM	Centre hospitalier de l'Université de Montréal
CSSS	Centres de santé et de services sociaux (Health and Social Services Centres)
ELISA	Enzyme linked immunoabsorbant assay
HpSA	Helicobacter pylori Stool Antigen Test
MALT	Mucosa-Associated Lymphoid Tissue
MSSS	Ministère de la Santé et des Services sociaux
NPV	Negative predictive value
NSAID	Non-steroid anti-inflammatory drugs
PPV	Positive predictive value
UBT	Urea breath test

GLOSSARY

Antibody

Specific molecule produced in the immune response to a given agent.

Antigen

Specific component of a particular agent involved in the immune response of a host.

Dyspepsia

Any episodic or persistent symptom or combinations of symptoms of pain or discomfort, referable to the upper gastrointestinal tract.

Negative Predictive Value

Probability of an individual actually not having the condition when test is negative (see Appendix A).

Positive Predictive Value

Probability of an individual actually having the condition when test is positive (see Appendix A).

Sensitivity

Ability of a test to correctly detect real cases of a given condition in the test population. Expressed as the number of affected individuals with positive tests divided by the total number of individuals with the condition in question (see Appendix A).

Specificity

Ability of a test to correctly detect cases that do not have the condition in question. Expressed as the number of individuals without the condition in question with a negative test result divided by the total number of individuals without the condition (see Appendix A).

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Helicobacter pylori, a rod-shaped bacterium, colonizes the mucus layer of the human stomach and is found in an estimated 20% to 40% of Canadians [Veldhuyzen van Zanten et al., 1994]. The discovery of *H. pylori* as a gastroduodenal pathogen [Warren and Marshall, 1983] is one of the major medical discoveries of the last 20 years, and has spurred much research and development of eradication therapies. Most infected persons are asymptomatic [Logan and Walker, 2001], however infection with *H. pylori* plays an important role in the development of gastritis, peptic ulcers, gastric cancers and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [Genta and Graham, 1997; Graham et al., 1992; Blaser, 1990; Morris and Nicholson, 1987]. In fact, the vast majority of duodenal and gastric ulcers are associated with *H. pylori* [Hunt and Thomson, 1998; Agréus and Talley, 1997].

At a consensus conference of the Canadian Helicobacter Study Group in May 2003, evidence was presented in favor of selective testing for *H. pylori* followed by eradication for certain groups of individuals following evidence-based guidelines [Hunt et al., 2004]. While exact clinical criteria for *H. pylori* testing and eradication therapy are evolving, the demand for testing for *H. pylori* will undoubtedly continue to rise in Canada.

Various invasive and non-invasive methods of detection of *H. pylori* infection exist, such as endoscopy and biopsy, serological testing, the stool antigen test and the urea breath test (UBT). The non-invasive UBT requires ingestion of labelled

urea followed by collection of samples of exhaled air from patients for analysis. The UBT is generally considered to be the preferred test for *H. pylori* detection [Veldhuyzen van Zanten et al., 2005; Chiba and Veldhuyzen van Zanten, 1999; Cohen et al., 1999; Hunt et al., 1999; Klein and Graham, 1993; Logan et al., 1991]. In Canada, however, use, availability, and public coverage of the UBT are unequal, varying between jurisdictions as well as between urban and rural areas, and this test is generally considered to be underused in practice [Romagnuolo et al., 2002; Fallone et al., 2000; Chiba and Veldhuyzen van Zanten, 1999]. Despite the existence of non-invasive tests for *H. pylori*, gastroscopy has often been the preferred diagnostic test among physicians in certain contexts [Maconi et al., 1999]. It is unclear to what extent this is the case currently in Québec, however lack of access to the UBT could indeed increase use of gastroscopy.

There are two types of UBT, radioactive (^{14}C -UBT) and non-radioactive (^{13}C -UBT). In Québec the ^{14}C -UBT is publicly covered and is administered only at certain hospitals with nuclear medicine departments. The ^{13}C -UBT has been included in the list of available public laboratory analyses in April 2005 [MSSS, 2005a]. At the request of the Québec Ministry of Health and Social Services, this technology brief examines the relevance of increasing utilization of the ^{13}C -UBT in the province of Québec for testing of patients with dyspepsia following evidence-based clinical guidelines.

The term dyspepsia generally refers to any episodic or persistent symptom or combinations of symptoms of pain or discomfort, referable to the upper gastrointestinal tract. Given the role of *H. pylori* in various disorders of the gastrointestinal tract, testing for *H. pylori* and treatment has an important role in the management of dyspepsia. Management approaches for the dyspeptic patient have been the object of numerous articles and published guidelines in recent years [Hunt et al., 2004; NICE, 2004], but the optimal approach is still the object of much debate [Bytzer, 2004]. Certain clinical circumstances, such as symptoms of more serious pathologies, warrant invasive diagnostic approaches [Hunt et al., 2004; Vaira and Vakil, 2001]. While early endoscopy remains the diagnostic gold standard, competing non-invasive strategies challenge this. One non-invasive approach involves empiric antisecretory treatment reserving endoscopy for unresponsive patients and patients with early symptomatic relapse. However, this strategy has been questioned, as there is recent concern that acid-suppressive medications are being overused in dyspeptic patients [Krol et al., 2004].

H. pylori-based strategies involve diagnosis of active infection followed by prescription of appropriate medication to eradicate these bacteria from affected individuals. Failures of eradication therapy are not uncommon; therefore in addition to the initial diagnostic test for *H. pylori*, clinicians often perform testing to confirm success of eradication following completion of therapy.

2.1 INVASIVE STRATEGIES USING ENDOSCOPY

When endoscopy is performed, biopsy samples of gastric mucosa may be tested to diagnose *H. pylori* infection and initiate eradication therapy when test results are positive. These tests can use differ-

ent methods such as histology and staining, urease tests or tissue culture to detect bacteria. While endoscopy is appropriate for certain populations and tends to be quite accurate in terms of diagnosis, it is generally expensive, impractical for the primary care physician, and can involve considerable discomfort for the patient. Since the potential overuse of endoscopy in the management of dyspepsia has been discussed in literature [McColl et al., 2002; Ofman and Rabeneck, 1999], there is interest in non-invasive tests for certain patient populations. This interest is increased by the fact that even when invasive diagnostic strategies are followed, non-invasive testing is often employed to confirm successful eradication of *H. pylori*.

2.2 NON-INVASIVE 'TEST-AND-TREAT' STRATEGY

A non-invasive strategy for which there is much interest is the 'test-and-treat' strategy. Non-invasive testing is used for diagnosis of *H. pylori* infection, followed by eradication therapy when results are positive. This approach has been well documented as being safe and cost-effective [Bytzer, 2004]. The American Gastroenterological Association [Talley et al., 1999], recent clinical guidelines [Veldhuyzen van Zanten et al., 2005; NICE, 2004; SIGN, 2003], and several international consensus conferences [EHPSG, 1997; Puera, 1997] endorse various versions of the 'test-and-treat' strategy for patients with uninvestigated, uncomplicated dyspepsia. However, certain populations are excluded from this approach, such as patients over the age of 50 with new symptoms, those who have predominant heartburn, or those who have alarm symptoms such as weight loss or bleeding in whom other diagnostics must be excluded. This selective approach is also recommended in Canadian guidelines for dyspepsia management [Veldhuyzen van Zanten et al., 2000]. This clinical management tool

(presented in Appendix B) would divert a certain number of patients now referred to endoscopy toward testing and eradication for *H. pylori*. In the absence of detailed data on endoscopy rates, the actual rate of endoscopies that could be avoided is difficult to quantify. The presence of waiting lists for endoscopy also complicates this issue.

Non-invasive testing for *H. pylori* has been shown to be as effective as endoscopy for patients less than 55 years of age with uncomplicated dyspepsia, and is much less uncomfortable and distressing for the patient [McColl et al., 2002]. Other publications have found testing and treatment of dyspeptic patients under 40 years of age to be cheaper than endoscopy [Gee et al., 2002; Jones et al., 1999], more effective [Heaney et al., 1999; Moayyedi et al., 1998], and also more cost-effective [Groeneveld et al., 2001]. In addition, a Cochrane analysis concluded that the ‘test-and-treat’ strategy is as effective as endoscopy-based management and that it reduces costs by decreasing

the number of patients that are endoscoped [De-laney et al., 2003]. However, some reports have indicated that a ‘test-and-treat’ strategy does not save endoscopy workload [Mahadeva et al., 2002].

The actual extent to which a ‘test-and-treat’ strategy would affect endoscopy use in Québec is therefore difficult to estimate. For example, it is unknown to what extent clinicians in Québec follow (or will follow, given greater availability of testing) guidelines involving the ‘test-and-treat’ strategy. In Europe, where similar guidelines exist, compliance by clinicians was found to be moderate, with endoscopy often being employed for diagnosis of *H. pylori* infection [Weijnen et al., 2001b] indicating the need for educational programmes for clinicians [Perri et al., 2002a]. Also, clinicians will generally initiate testing and eradication therapy if they consider this strategy to be feasible and desirable for an individual patient [Hardin and Wright, 2002].

Non-invasive *H. pylori*-based strategies are important in the management of dyspepsia and testing methods have a central role, whether the goal is to diagnose infection or confirm eradication of *H. pylori*. Various advantages and disadvantages of non-invasive tests that are currently available in Québec must therefore be evaluated in terms of sensitivity, specificity, availability, ease of use, and cost. Non-invasive tests include antibody tests (serum, saliva or whole blood), antigen tests (stool, saliva or urine), or urea breath tests (radioactive or non-radioactive).

3.1 ANTIBODY TESTS

These tests do not directly detect the presence of *H. pylori* but rather the presence of an immune response to *H. pylori* in the form of antibodies. These antibodies may persist even after successful eradication (when *H. pylori* infection is no longer present). Saliva and whole blood tests can be conveniently done in the office setting, but they have lower diagnostic accuracy than serum tests [Loeb et al., 1997; Fallone et al., 1996] and are therefore not recommended [Chiba and Veldhuyzen van Zanten, 1999].

Antibody serum tests include a number of different techniques such as enzyme linked immuno-adsorbant assays (ELISA), western blotting and agglutination tests. A meta-analysis of 21 studies using ELISA serology kits indicated overall sensitivity of 85% and specificity of 79% [Loy et al., 1996].

Given that antibody levels persist for long periods of time, the frequency of false positive tests will increase with the number of patients who are treated. Overall, the major disadvantage of serology is that antibodies to *H. pylori* and not actual infection are documented [Chiba and Veldhuyzen van Zanten, 1999], limiting its positive predictive value and application to confirm successful eradication of *H. pylori*.

3.2 ANTIGEN TESTS

Antigen detection in saliva [Luzza et al., 2000] or urine [Miwa et al., 1999] are other potential testing methods, however work is preliminary. Current interest focuses mainly on the stool antigen test (HpSA), an in vitro qualitative procedure for the detection of *H. pylori* antigens in human stool tested by enzyme immunoassay technique.

The HpSA offers elevated sensitivity and specificity rates [Vaira et al., 2002; Konstantopoulos et al., 2001; Monteiro et al., 2001], estimated at 93% and 92% respectively [Vaira and Vakil, 2001]. In addition, ease of sample collection in very young children is another proposed advantage [Ni et al., 2000], as is the potential for lower cost than that of other available tests [Braden et al., 2000]. Some authors anticipate that the HpSA will challenge other available testing methods [Monteiro et al., 2001; Trevisani et al., 1999]. However, the HpSA has been reported to be less reliable for post-treatment testing [Bilardi et al., 2002; Cullen et al., 2002; Perri et al., 2002b]. In addition to key issues of compliance, ease of use, and clinician and patient preferences, there are important questions regarding interlaboratory variability and test performance for this test [Cullen et al., 2002; Braden et al., 2000; Weir, 2000].

3.3 THE UREA BREATH TEST

The urea breath test (UBT) for *H. pylori* is a non-invasive diagnostic procedure utilizing analysis of breath samples to determine the presence of active *H. pylori* infection in the stomach. This test is based on the high urease activity of this organism, which readily hydrolyses urea to carbon dioxide (CO₂) and ammonia (NH₄), and consists of analysis of breath samples before and after ingestion of labelled C-urea. There are two methods for labelling the urea used in the breath test: one is to use the stable heavy isotope ¹³C and the other is to use the radioactive isotope ¹⁴C.

Proper preparation is crucial. Patients must abstain from taking medications that alter bacterial load (such as antibiotics, bismuth, proton pump inhibitors, antacids and H₂ antagonists) for various periods up to one month preceding the test [Desroches, 2001] and must fast for three hours before undergoing the test. Patients first consume a solution of citric acid to delay the stomach from emptying during the test. The patient blows through a straw into a glass tube that collects a reference breath sample. They then consume a drink containing the labelled urea, which will decompose to form labelled CO₂ and NH₄ in the presence of urease that is produced by *H. pylori* in the stomach. The labelled CO₂ is absorbed in the blood, then exhaled in the breath. After 30 minutes, a second breath sample is taken, which is analyzed and compared with the baseline breath sample obtained before the ingestion of the labelled C-urea. The breath sample can easily be stored at various temperatures over several days. Increased amounts of the labelled CO₂ indicate the presence of *H. pylori*, and the magnitude of the increase of labelled CO₂ indicates the extent of active infection [Berger, 2002].

The UBT has been observed to have sensitivity and specificity values of about 95%, which has been well documented in numerous publications and review articles [Gomollón et al., 2003; Vaira et al., 2002; Monteiro et al., 2001; Logan and Walker, 2001; Ni et al., 2000; Chiba and Veldhuyzen van Zanten, 1999; Cohen et al., 1999; McNamara et al., 1999; Miwa et al., 1998; Bazzoli et al., 1997; Cutler et al., 1995; NIHCDP, 1994]. For example, weighted averages of 94.7% sensitivity and 95.7% specificity were observed in 3653 patients studied in 1999–2000 [Vaira and Vakil, 2001]. The radioactive (¹⁴C) and non-radioactive (¹³C) versions of the UBT are equally accurate [Atherton, 1997].

3.4 COMPARISON OF NON-INVASIVE TESTING METHODS

There are currently three key types of non-invasive testing in Québec: serology, the stool antigen test (HpSA), and the urea breath test (UBT). Some advantages and disadvantages of each test are presented in Table 1.

TABLE 1

Advantages and disadvantages of key non-invasive testing methods for <i>H. pylori</i>			
NON-INVASIVE METHODS	DISADVANTAGES	ADVANTAGES	AVAILABILITY/PUBLIC COVERAGE IN QUÉBEC
Antibody: Serology	<ul style="list-style-type: none"> ▪ High rate of false positives ▪ A positive result does not necessarily indicate active infection ▪ Not suitable to confirm eradication post-therapy 	<ul style="list-style-type: none"> ▪ Availability ▪ Low cost ▪ Negative result excludes <i>H. pylori</i> infection 	<ul style="list-style-type: none"> ▪ Widely available in public laboratories
Antigen: Stool antigen test (HpSA)	<ul style="list-style-type: none"> ▪ Variable performance post-eradication ▪ Patient and clinician preferences 	<ul style="list-style-type: none"> ▪ Good accuracy 	<ul style="list-style-type: none"> ▪ Not publicly covered, not widely available
Urea breath test	<ul style="list-style-type: none"> ▪ Requires specialized equipment for analysis ▪ Difficulty in obtaining breath samples from very young children 	<ul style="list-style-type: none"> ▪ Accuracy ▪ Standardization ▪ Ease of test administration 	<ul style="list-style-type: none"> ▪ Radioactive version available in several hospitals with nuclear medicine departments across Québec ▪ Non-radioactive version included in the list of available public laboratory analyses since April 2005, however not yet widely used

Adapted from: de Korwin, 2003.

Serology is mainly of interest because it is widely available and inexpensive. However, this indirect method of testing only indicates antibodies to *H. pylori* and not active infection, limiting the value of a positive test result and its positive predictive value (see Appendix A). This implies that there is little certitude that patients testing positive with serology actually have the infection and that further testing and/or investigation are required to confirm infection. Despite this major limitation, serology could be potentially useful in populations having a very low prevalence of *H. pylori* infection to exclude infection when test results are negative [SIGN, 2003]. However, the group of patients presenting to primary care with dyspepsia would generally be expected to have a much higher prevalence of *H. pylori* infection than the general population. Overall, the usefulness of serology is limited by uncertainty in interpretation of a positive test result.

In contrast, the stool antigen test (HpSA) can detect active infection and has generated significant interest in recent years. Sensitivity and specificity values approach that of the UBT. However, there are concerns about practicality and patient compliance, and more research on test performance is needed. The Canadian Helicobacter Study Group

recently concluded that there is currently insufficient evidence to consider stool antigen tests an acceptable tool for the diagnosis of *H. pylori* infection in community-based practice [Hunt et al., 2004]. Despite this, it is possible that the HpSA will become a valid option in the future, for example for young children who cannot correctly perform the procedure for the UBT.

The remaining option is the UBT, which is generally considered to be the preferred test for *H. pylori* detection [Chiba and Veldhuyzen van Zanten, 1999; Cohen et al., 1999; Hunt et al., 1999; Klein and Graham, 1993; Logan et al., 1991]. The UBT is often used as a non-invasive ‘gold standard’, since a breath test samples the whole stomach and gastric urease is only present when there are bacteria in the stomach that produce urease [Feldman and Evans, 1995]. The UBT is popular due to its ease of use and high diagnostic performance [Logan, 1998]. It has also been found to significantly decrease the inappropriate use of antimicrobial therapy compared with antibody testing [Chey and Fendrick, 2001]. In addition, it could be used more often in cases where symptoms persist after treatment and it is necessary to determine if infection is still active [Delchier, 2000]. The following section will compare the radioactive and non-radioactive versions of the UBT in detail.

COMPARISON OF RADIOACTIVE AND NON-RADIOACTIVE VERSIONS OF THE UBT

The non-radioactive ^{13}C and radioactive ^{14}C versions of the urea breath test (UBT) differ only in the method used to label carbon atoms (weight or radioactivity), test performance being virtually identical [Atherton, 1997]. Therefore, practical rather than theoretical considerations determine which test is preferred in a given context for a given patient [Wong et al., 1997]. These tests can be compared with regard to their current use and availability, accessibility and settings for test administration, requirements for test analysis, eligible patient populations, and cost of testing.

4.1 CURRENT USE AND AVAILABILITY

The ^{14}C -UBT uses a radioactive isotope of carbon with a half-life of 5730 years [Cutnell and Johnson, 1995]. This test is publicly covered in Québec and accounts for the vast majority of UBTs currently administered. The ^{13}C -UBT is publicly covered in countries such as France [Delchier, 2000], in certain Canadian jurisdictions such as British Columbia and Alberta¹, and has been only included in the list of available public laboratory tests in Québec in April 2005. Actual volume of use of the ^{14}C -UBT in Québec is unknown, but consultations by the author indicated that some larger hospitals in Montréal had a volume of tests over 1000 in 2003, many of which were for confirmation of *H. pylori* eradication following treatment. A growing number of hospitals with nuclear medicine departments are using the ^{14}C -UBT (approximately 50 across the province²), and yearly volume of tests is increasing where it is offered. The lack of public coverage has, up to now, limited the use of the ^{13}C -UBT to private laboratories,

a few hospitals, and to medical clinics in isolated regions such as Northern Québec³. Despite the addition of the ^{13}C -UBT to the list of approved laboratory tests in April 2005, only two pediatric hospitals in Montréal have been identified to date as offering the test. Recent recommendations indicate that the ^{13}C -urea breath test is the best non-invasive test for detection of *H. pylori* infection in children [Jones et al., 2005].

4.2 ACCESSIBILITY AND SETTINGS FOR TEST ADMINISTRATION

The radioactive ^{14}C -UBT is only administered in certain hospitals with nuclear medicine departments that have developed the expertise to perform this test. Given that several smaller regional hospitals and health centres do not have nuclear medicine departments, patients in these areas do not have access to the ^{14}C -UBT. In contrast, the ^{13}C -UBT can be administered in remote regions and mailed to the manufacturer or to hospitals for analysis by mass spectrometry, which constitutes a major advantage compared to the radioactive version of the UBT. However, the dose of radioactivity in the ^{14}C -UBT is sufficiently low (less than 1/10 that of an x-ray [Desroches, 2001]), that some experts have proposed that administration could potentially occur outside nuclear medicine departments. While this is certainly theoretically possible, there is no evidence to date that current restrictions will change for this test.

Whether the test is administered in a hospital setting or elsewhere, it is important to ensure that a standard procedure is followed so that the test is administered properly (for example, that patients be adequately informed of which medications must be avoided in the weeks prior to test admin-

1. Calgary Laboratory Services (CLS), personal communication, May 2005.

2. Dr. D. Picard, CHUM, personal communication, March 2005.

3. Rad Diagnostics, Montréal, Québec, personal communication, May 2005.

istration). This requires that personnel be properly trained on how to administer this test. It is therefore recommended that the test be administered in the relatively controlled environment of a hospital or a CSSS⁴ to ensure proper patient preparation and test administration.

4.3 REQUIREMENTS FOR TEST ANALYSIS

For the ¹⁴C-UBT, analysis of samples is generally conducted in the hospital where the test was administered, using a β -scintillation counter. Some hospitals with small nuclear medicine departments may send samples to larger hospitals for analysis. For the ¹³C-UBT, a mass spectrometer is required for analysis; samples can be either mailed to the manufacturer who then returns test results or analyzed in a hospital equipped with a mass spectrometer.

4.4 ELIGIBLE PATIENT POPULATIONS

The ¹⁴C-UBT is generally contra-indicated for children and pregnant women. However, the dose of radioactivity is sufficiently low that some experts have questioned these contra-indications. For instance, it has been reported that ¹⁴C-UBTs with lower radiation activity levels could be used safely in children [Gunnarsson et al., 2002]. The limitations for the radioactive test could potentially be overcome in the near future. Despite these arguments for the safety of low-dose radioactivity, it is doubtful that a radioactive test be used routinely for pregnant women in non-urgent situations in current clinical practice in Canada. In contrast, the ¹³C-UBT can be used in these patient groups and can be a useful tool for diagnosis in pediatric populations who are of sufficient age to provide a breath sample [Jones et al., 2005; Deslandres, 1999].

4. CSSS: Centres de santé et de services sociaux. Created in 2005 by merging local community health centres (CLSCs), residential and long-term care centres (CHSLDs), and general and specialized hospital centres (CHSGSs).

4.5 COST

Actual unitary costs for these tests are difficult to estimate for the Province of Québec. However, standard values (technical units, weighted value) are assigned to both tests in provincial reference documents. The MSSS assigns 45 technical units in nuclear medicine to the ¹⁴C-urea breath test [MSSS, 2005b], while the weighted value of the ¹³C-urea breath test is equal to 40 [MSSS, 2005a]. While the monetary value of these units varies between hospitals, one can estimate that the costs of the two types of test are in a similar dollar range. For example, the current value of one technical unit in nuclear medicine at the CHUM (Hôpital Saint-Luc) is \$1.23⁵, which gives a cost of \$55.35 for the ¹⁴C-urea breath test. Each unit of the weighted value for biochemistry laboratory tests is equal to \$1, which gives a value of \$40 for the ¹³C-urea breath test. In both cases, salaries of professionals are excluded.

A Canadian economic evaluation conducted in 2000 evaluated the average cost of the ¹³C-urea breath test at \$66 (between \$40 and \$120). This cost included the cost of purchase of a mass spectrometer (amortized over 10 years with a 5% interest rate), as well as fixed annual costs (salary of technician, overhead costs, and laboratory costs) and variable costs (test kits, sample collection, shipping of tests to central laboratory for analysis). The average cost per test was calculated from analysis of 5000 samples [Marshall et al., 2000]. In another Canadian study, Chiba and Veldhuyzen van Zanten [1999] estimated the cost of test kits to be from \$45 to \$85. An economic analysis of the test-and-treat strategy estimated the cost of the ¹³C-urea breath test at \$80 in Canada, based on the cost billed by an Ontario laboratory [Chiba et al., 2002]. In Alberta, the test is now publicly covered for patients 18 years of age or older [AMA, 2005]; however before April 1, 2005, patients were billed \$75 to \$100⁶ [CLS, 2004].

5. Financial Statement AS-471, 2003–4, MSSS.

6. MDS Diagnostic Services, Montréal, Québec, personnel communication, 2004.

In British Columbia, ^{13}C -UBTs are administered by private laboratories and reimbursed by the Ministry of Health. The purchase cost for the test only is approximately \$20 to \$25 (depending on volume), and each test administered in private laboratory clinics is reimbursed at \$55 to \$57 (all costs included)⁷. There are at least two test manufacturers in Canada (Rad Diagnostics, Montréal, Québec; Isotechnika, Edmonton, Alberta), and prices should continue to decrease (as they have in recent years) as the market for this test develops internationally [McNulty et al., 2005].

Overall costs for the two tests are much lower than the more invasive endoscopic procedures as indicated in the literature. For example, a publication released in 2002 estimated the cost of an endoscopy for a sedated, biopsied patient in Québec to be from \$154 to \$217, depending on whether non-reusable biopsy forceps were used, plus \$41 in hospital overhead costs [Crott et al., 2002]. Because these costs depend on context and volume of testing, they cannot be predicted in great detail without actual comparative field evaluation.

Cost savings are possible by enabling appropriate treatment of problems related to *H. pylori* at an early stage, thereby avoiding referrals to specialists and potentially preventing more serious and costly health problems. Another potential cost savings to be considered from a societal perspective would be avoided travel costs for patients if the ^{13}C -UBT can be administered closer to their places of residence, especially in isolated regions.

4.6 OVERALL COMPARISON OF THE ^{14}C - AND ^{13}C -UBT

Overall, we see that the ^{14}C - and ^{13}C -UBTs are very similar, proven tests currently recognized as the best non-invasive tests for detection of *H. pylori* infection. The two tests can be considered as equally effective [Atherton, 1997]. At present in

Québec, the major difference is that the ^{14}C -UBT is increasingly used in numerous hospitals, while the ^{13}C -UBT is less widely used. The differences between the two tests are summarized in Table 2.

Significant differences between the two tests are few. The fact that the use of the ^{14}C -UBT is well established in numerous centres is an advantage. In contrast, the ^{13}C -UBT could have the advantage of serving populations who do not currently have access to the UBT. In theory, another advantage of the ^{13}C test would be to free up resources in nuclear medicine departments functioning at full capacity because testing can occur directly in the primary care setting. The ^{13}C -UBT could allow savings for patients in avoiding the time and expense of travelling to a hospital with nuclear medicine facilities. The fact that ^{13}C -UBT test samples may be mailed to a hospital for mass spectrometry analysis also implies certain costs and processing, but the process appears to be relatively simple, with results being returned quickly by e-mail or fax. This aspect of the ^{13}C -UBT is difficult to evaluate without actual field evaluation.

Given that the ^{14}C -UBT is radioactive, special storage and handling measures are required as well as informed consent from patients. In addition, some patients may prefer a non-radioactive alternative.

Overall, we see that the ^{14}C -UBT has the advantage of being a test that is currently in systematic use in a controlled setting in Québec. However, access is limited, both in geographic terms and because certain patient populations are not eligible for a radioactive test. If the ^{13}C -UBT is indeed as easy to administer as is expected, at costs similar to projected values, and if it can be properly administered in CSSS and their service points, significant use and benefit is to be expected if the test is made available in all regions of Québec.

The two types of UBT are therefore likely to be complementary. In the long term, the two tests will probably compete with one another, and the choice will depend on cost and practical consider-

7. Isotechnika Inc, Edmonton, Alberta; personal communication, March 2005.

ations for a given region. While there are various predictions as to the exact proportion of ^{14}C - and ^{13}C -UBT that would be used should both tests be available throughout the province, this is of little importance compared to the larger goal of increas-

ing accessibility to the UBT for the population of Québec. In this respect, both tests can be expected to have a useful place in the array of tests available in Québec's public health-care system.

TABLE 2

Comparison of the ^{14}C- and ^{13}C-UBT		
ASPECT	^{14}C -UBT	^{13}C -UBT
Sensitivity and specificity	$\approx 95\%$	$\approx 95\%$
Place of administration	Hospitals with nuclear medicine departments	Any location in which test can be given properly
Analysis	In hospital with nuclear medicine department and β -scintillation counter	Mass spectrometry analysis (in a hospital or mailed to the manufacturer)
Radioactive	Yes	No
Public coverage in Québec	Yes, in hospitals (global budget)	Yes, in public laboratories (global budget), but not widely used
Patient populations	Not suitable for children or pregnant women	Not suitable for very young children

Use of the ^{14}C -UBT is expanding in Canada, particularly in Québec where the test is administered in public hospitals. The ^{13}C -UBT is publicly covered in British Columbia, Alberta and Québec (since April 1st, 2005). However, it is not covered in other Canadian provinces, despite its definite advantages in terms of ease of administration, and accessibility to a larger percentage of patients over a larger geographical area. Estimated cost of the ^{13}C -UBT is in a range similar to that of the ^{14}C -UBT.

There is little information about the current clinical practice regarding the management of dyspepsia in Québec, the differences in practice between urban and rural settings, the availability of endoscopy, and the availability of UBT in the region of treatment. It is possible that increased access to the ^{13}C -UBT could significantly reduce the number of endoscopies for patients in regional settings as well as the associated costs to the health-care system and distress to patient caused by discomfort and travel.

There has been concern that greater accessibility to the ^{13}C -UBT will cause indiscriminate testing. However, the ^{14}C -UBT is already available to physicians, and literature has indicated that the UBT is often underused compared to endoscopy in clinical practice [Weijnen, 2001b]. Current guidelines encourage a systematic, evidence-based process with testing of only those who will benefit. In addition, clinicians can be expected to take local factors into account as well as the context of each patient.

Requiring users of test to report data on patient characteristics (age, sex, symptoms) and context of use (diagnosis or confirmation of eradication), as well as periodic overall evaluation of *H. pylori* testing in Québec (i.e. on a yearly basis) would help to evaluate and improve appropriateness of use of this test. Optimal diagnostic strategies for *H. pylori* infection should also be periodically re-evaluated in light of developments in diagnostic technologies (cost, ease of use, performance), epidemiology of *H. pylori* infection, and optimal management strategies for dyspepsia.

Overall, the ^{13}C -UBT is a diagnostic technology whose efficacy is well proven, easy to administer at a reasonable cost. It has the potential to be a useful test that can improve the quality of dyspepsia management for the numerous patients who suffer from this disorder across Québec, particularly those outside urban areas. In addition, this test has the potential to be cost saving by avoiding other health-care interventions. Correctly administered, it presents definite advantages in accessibility compared with the ^{14}C -UBT.

While the prevalence of *H. pylori* infection and related diseases seems to be decreasing in Canada, the prevalence of infection remains substan-

tial in many areas [Hunt et al., 2004]. Specific prevalence in Québec needs to be studied.

The ^{13}C -UBT has recently been added to the list of laboratory tests available in public laboratories in Québec, and increased availability is justified due to the fact that it can be offered in geographic areas and patient populations for which the ^{14}C -UBT is not available. If use of the UBT expands greatly, some health-care settings may have the choice of either test. In this case field evaluation could be conducted to examine advantages of each test in terms of cost and administration in particular settings.

Access to the ^{13}C -urea breath test in all regions of the Province of Québec is recommended, with the following proposals for optimal use of this test:

- Patients in public health-care institutions in all regions should have access to the ^{13}C -urea breath test.
- Centres that administer the ^{13}C -urea breath test must respect proper procedures and ensure quality control.
- Clinicians should be informed of the availability of this test.
- Clinicians involved (gastroenterologists, pediatricians, general practitioners) should define optimal use of this test for diagnosis and confirmation of eradication of *H. pylori* in current clinical practice.
- Due to the expected evolution of various testing options for *H. pylori*, developments in all types of invasive and non-invasive testing in this area should be periodically re-evaluated in collaboration with experts in this area in Québec (members of the Canadian Helicobacter Study Group, for instance).

APPENDIX A

DETERMINING TEST PERFORMANCE

This section explains the concepts of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) that are required to compare various diagnostic tests for *H. pylori*.

		INDIVIDUALS		TOTAL
		INFECTED WITH <i>H. PYLORI</i>	NOT INFECTED WITH <i>H. PYLORI</i>	
Test result	+	TP	FP	TP + FP
	-	FN	TN	FN + TN
Total		TP + FN	TN + FP	TP + FP + TN + FN

TP (true-positive): Individual is infected with *H. pylori* and the test result is positive; FP (false-positive): Individual is not infected with *H. pylori* and the test result is positive; FN (false-negative): Individual is infected with *H. pylori* and the test result is negative; TN (true-negative): Individual is not infected with *H. pylori* and the test result is negative.

$$\text{Sensitivity} = \text{TP} / (\text{TP} + \text{FN}) \times 100$$

The sensitivity of a test is the proportion of all affected individuals that the test is able to detect in the population.

$$\text{Specificity} = \text{TN} / (\text{TN} + \text{FP}) \times 100$$

The specificity of a test is the proportion of unaffected individuals confirmed not to have the disease by a negative test result. The complement of specificity, *1-specificity*, is the proportion of false-positive results.

$$\text{Positive predictive value (PPV)} = \text{TP} / (\text{TP} + \text{FP}) \times 100$$

The positive predictive value is the probability of having the disease when the test result is positive. For *H. pylori* testing, this refers to the proportion of patients testing positive for *H. pylori* who actually have the infection. This can also be expressed as the ratio of true positives to total positive tests, meaning the proportion of patients with positive test results who are correctly diagnosed.

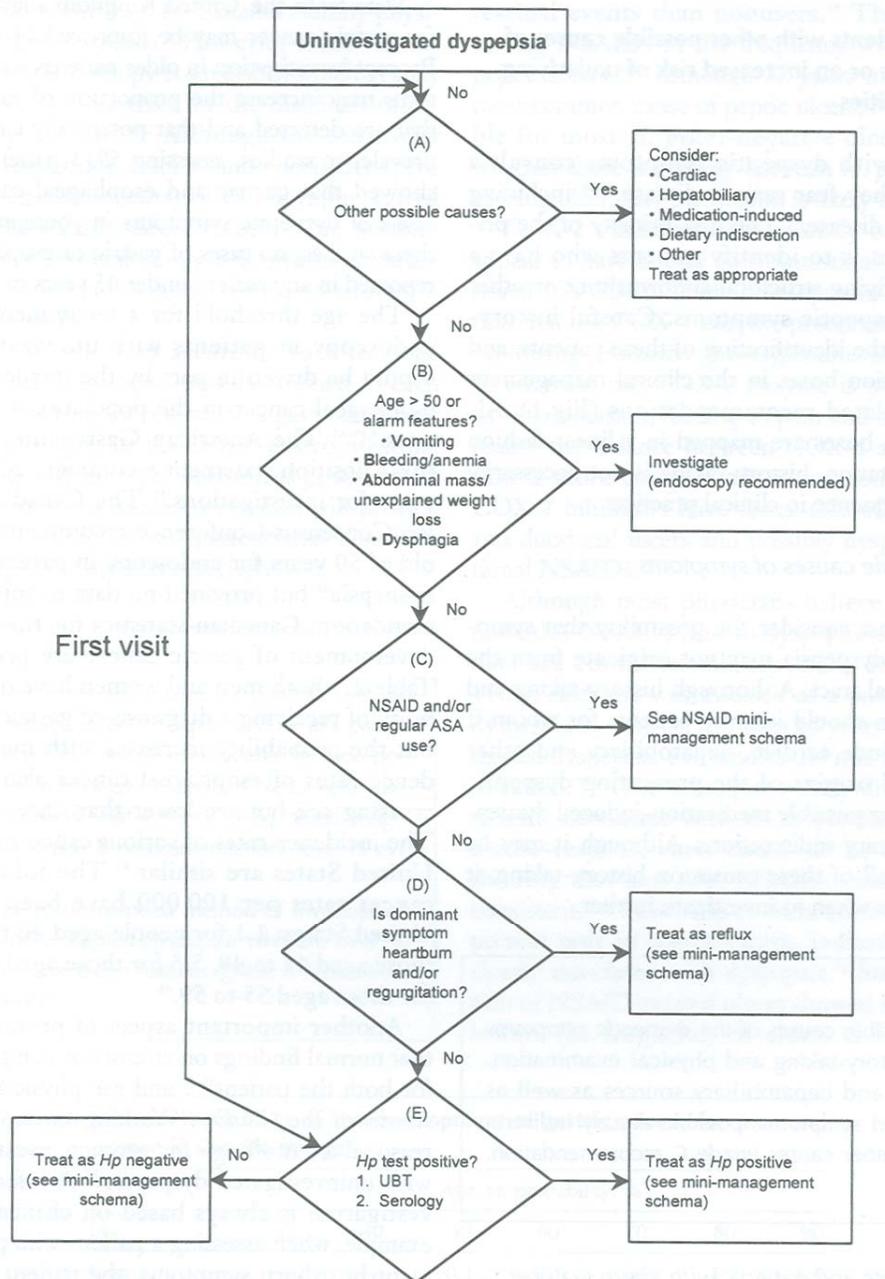
$$\text{Negative predictive value (NPV)} = \text{TN} / (\text{TN} + \text{FN}) \times 100$$

The negative predictive value of a test is the probability of not having the disease when the test result is negative. For *H. pylori* testing, this refers to the proportion of patients testing negative for *H. pylori* who actually do not have the infection. This can also be expressed as the ratio of true negatives to total negative tests, meaning the proportion of patients with negative test results who are correctly diagnosed.

Adapted from Feldman and Evans, 1995; Jenicek, 1995; Hennekens and Buring, 1987.

APPENDIX B

CANADIAN CLINICAL MANAGEMENT TOOL FOR PATIENTS WITH UNINVESTIGATED DYSPEPSIA IN PRIMARY CARE



Source: Veldhuyzen van Zanten et al., 2000.

Hp: *Helicobacter pylori*; UBT: Urea breath test.

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