Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Serum Vitamin B12 Testing: A Rapid Review

Health Quality Ontario

December 2012

Serum Vitamin B12 Testing: A Rapid Review. December 2012; pp. 1–16.

Suggested Citation

This report should be cited as follows:

Health Quality Ontario. Serum vitamin B12 testing: a rapid review. Toronto, ON: Health Quality Ontario; 2012 Dec. 16 p. Available from: www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy makers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Permission Requests

How to Obtain Rapid Reviews From Health Quality Ontario

All rapid reviews are freely available in PDF format at the following URL:
http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Table of Contents

Background

Objective of Analysis

The objective of this rapid review was to establish under what circumstances, and how often, serum vitamin B12 tests should be used to assess vitamin B12 deficiency.

Clinical Need and Target Population

Description of Vitamin B12 Deficiency

Vitamin B12 is a water-soluble, essential vitamin. A deficiency in vitamin B12, which can occur due to inadequate absorption or intake, can lead to neurological, psychiatric, and hematological disorders. Foods that contain vitamin B12 include dairy and meat products. As a result, long-term vegans are at a higher risk of deficiency than others, and need to ensure they are choosing foods fortified with vitamin B12 or taking supplements. Vitamin B12 is stored for years in the liver, and a deficiency in vitamin B12 can occur slowly over time if B12 stores are depleted.

Causes of Vitamin B12 Deficiency

There are 3 main reasons a person becomes vitamin B12 deficient: (1)

- Inadequate dietary intake of vitamin B12
  - Strict vegetarianism (over the long term)
- Ineffective gastric breakdown of vitamin B12
  - Bacterial overgrowth syndromes
  - Fish tapeworm infestation
- Malabsorption of vitamin B12
  - Pernicious anemia
  - Gastrectomy or gastric bypass
  - Protein-bound cobalamin malabsorption
  - Ileal disease or resection
  - Pancreatic insufficiency
  - Drug induced (colchine, neomycin, p-aminosalicylic acid, omeprazole)

Prevalence of Vitamin B12 Deficiency

It is unclear what the prevalence of vitamin B12 deficiency is in the general population. However, it is estimated to be between 2% and 6% in the United States. (2) Vitamin B12 deficiency is defined as a serum vitamin B12 level of less than 148 pmol/L. The prevalence of vitamin B12 deficiency is somewhat higher among the elderly (6-12%), (3;4) with an even higher prevalence among sick or institutionalized elderly (30-40%). (4) The prevalence of subnormal vitamin B12 levels (defined as a serum level between 148 pmol/L and 221 pmol/L) was estimated by 1 study to be around 20% in the elderly U.S. population. (3) Another study, however, based on the Framingham Offspring Study, reported that up to 39% of the U.S. population had subnormal serum vitamin B12 levels. (5)

Ontario Context

In the 2010/2011 fiscal year, more than 2.9 million serum vitamin B12 laboratory tests were billed to the province, at a cost of roughly $40 million. This was an increase over the number of tests performed in the 2005/2006 fiscal year, and was particularly marked in the community setting. (Table 1, Figure 1). One possible contributing factor was that, in 2007, the vitamin B12 test was added to the physician laboratory requisition form. The number of lab tests for vitamin B12 jumped by nearly 1 million between 2007 and 2008.

Table 1: Volume of Vitamin B12 Laboratory Tests in Ontario from 2005 to 2010

Fiscal Year	Hospital	Community	Total
2005	173,284	1,083,219	1,256,503
2006	199,412	1,188,066	1,387,478
2007	206,917	1,509,800	1,716,717
2008	222,136	2,436,765	2,658,901
2009	247,746	2,865,684	3,113,430
2010	255,620	2,651,992	2,907,612

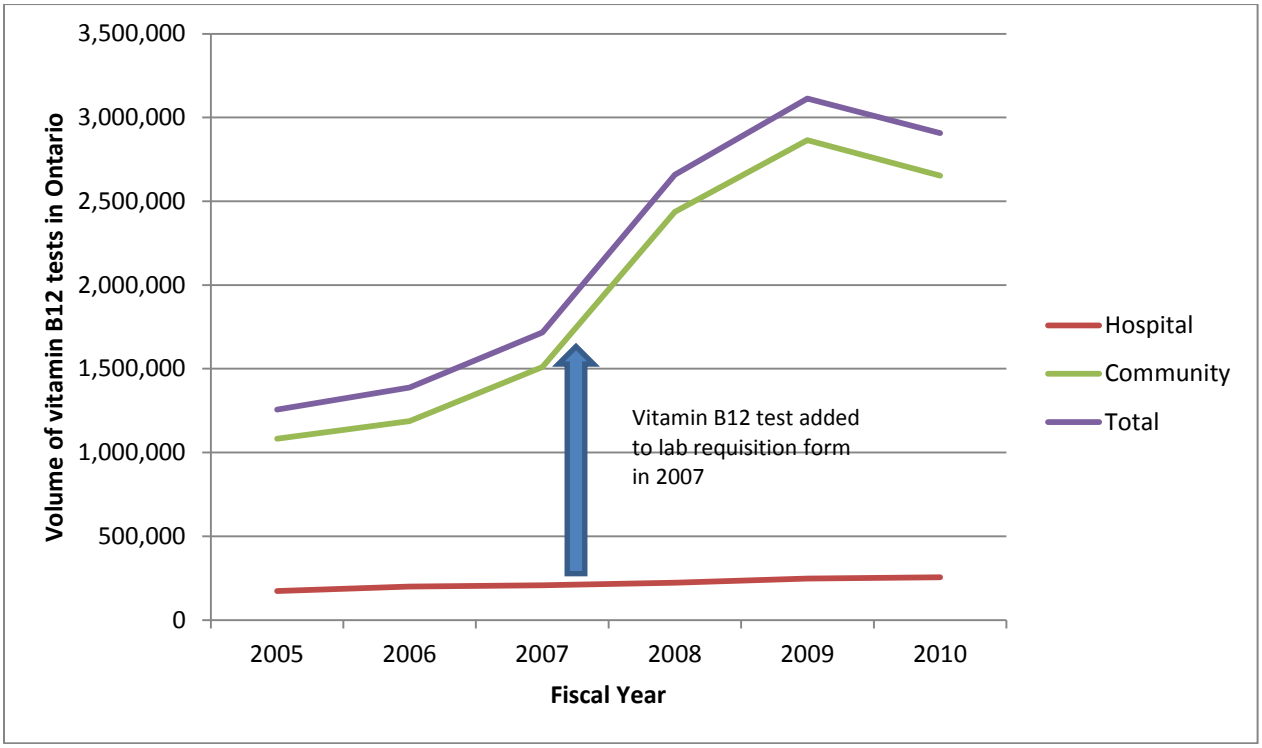

Figure 1: Volume of Vitamin B12 Tests in Ontario from 2005 to 2010

Rapid Review

Research Questions

1. Who should be tested for vitamin B12 deficiency?
2. How frequently should patients with vitamin B12 deficiency be tested?

Research Methods

Literature Search

A literature search was performed on June 28, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2000, until June 28, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language reports
- published between January 1, 2000, and June 28, 2012
- systematic reviews, meta-analyses, and clinical practice guidelines
- investigated the assessment of measuring vitamin B12 levels

Exclusion Criteria

- studies investigating treatment or interventions for vitamin B12 deficiency
- randomized controlled trials, observational studies, case series, or editorials
- non–English language studies

Expert Panel

In August 2012, an Expert Advisory Panel on Appropriate Use of Vitamin B12, Folic Acid, and Iron Testing was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representatives from community laboratories.

The role of the Expert Advisory Panel on Appropriate Use of Vitamin B12, Folic Acid, and Iron Testing was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of vitamin B12, folic acid, and iron testing in the Ontario health care system. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Results of Literature Search

The database search yielded 2,120 citations published between January 1, 2000, and June 28, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

In 2011, Willis et al (6) published a systematic review and meta-analysis of the diagnostic accuracy of the serum tests for assessing vitamin B12 (or cobalamin). They searched the literature from 1990 to 2009 and identified 54 studies for inclusion. They reported that there was no consistent reference standard used to measure the accuracy of the serum vitamin B12 test. They also reported a wide range of variability for sensitivity and specificity across the studies. For sensitivity, the range was 13% to 75%, and for specificity it was 45% to 100%. The authors (6) attributed the wide ranges to the inconsistent use of a reference standard.

Hvas and Nexo (7) also published an article regarding the diagnostic accuracy of serum vitamin B12 testing. Although their review was not systematic, they described the strengths and weaknesses of each vitamin B12 serum test. A summary of the tests based on the review of Hvas and Nexo (7) is listed in Table 2.

Table 2: Summary of Laboratory Tests Used to Assess Vitamin B12 Deficiency

Laboratory Test	Rationale for Using the Test	Advantages	Disadvantages
Cobalamin	Decreases in vitamin B12 deficiency	Easily accessible $10 to $15 per test (in Ontario)	Sensitivity and specificity are questionable
Methymalonic acid (MMA)[a]	Increases with vitamin B12 deficiency	High sensitivity	Questionable specificity Roughly $105 per test
Total homocysteine (Hcy)[a]	Increases with vitamin B12 deficiency	High sensitivity	Low specificity influenced by lifestyle factors (smoking, alcohol consumption, coffee consumption) Roughly $65 per test
Holotranscobalamin (holoTC)[a]	Decreases in vitamin B12 deficiency Newer test, clinical utility unclear	High sensitivity	Specificity unclear

[a]These laboratory tests are uninsured in community laboratories.

Three guidelines were identified on the diagnosis of vitamin B12 deficiency. There are countless guidelines on other conditions which indicate that serum vitamin B12 should be accessed, including but not limited to those for cognitive impairment (8), dementia (9), and Crohn's disease (10).

The three guidelines (4;11;12) were assessed using the AGREE appraisal tool. (13) The assessment for each guideline is summarized in Table 3. Two of the guidelines were systematic reviews with recommendations. (4;12) These 2 reviews were published in peer-reviewed journals and described their methodology for the systematic literature search. The guideline by the British Columbia Medical Association and Ministry of Health was not explicitly based on a systematic review of the literature. In the methods that are reported on the website that published the guideline, the authors state that a full systematic review may not be conducted for all of their guidelines. As a result, it is unclear whether this guideline was based on the results of a systematic review. The British Columbia guidelines group has been contacted for further clarification.

All 3 guidelines scored poorly on linking the evidence to the recommendations.

Table 3: AGREE Appraisal Summary for Each Guideline

Guideline	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence
British Columbia Medical Association/ Ministry of Health, 2012 (11)	11	3	18	17	4	3
Smellie et al, 2005 (12)	17	20	34	21	7	5
Andres et al, 2004 (4)	10	6	27	21	5	3

The recommendations from each of the guidelines are listed in Table 4. The systematic review by Andres et al (4) used a flow chart or care pathway to describe recommendations. A notable difference in the guideline by Andres et al (4) was that the authors recommended screening all patients in institutions or psychiatric hospitals for vitamin B12 deficiency. This was not a factor in either of the other guidelines. Andres et al (4) reported that the prevalence of vitamin B12 deficiency was much higher (30% to 40%) in patients who were sick or institutionalized. As mentioned above, there was a very weak relationship between the recommendations and the evidence presented in all guidelines.

Table 4: Guidelines for the Assessment of Vitamin B12 Levels

Guideline	Populations for Testing	Frequency	Overall Recommendation
British Columbia Medical Association/ Ministry of Health, 2012 (11)	Patients with unexplained neurologic symptoms (parasthesia, numbness, poor motor coordination, memory lapses) Patients with macrocytic anemia or macrocytosis	Not reported	Routine screening for vitamin B12 deficiency is not recommended
Smellie et al, 2005 (12)	Patients with macrocytic anemia Patients with macrocytosis Patients with specific neuropsychiatric abnormalities	"There is no obvious merit in repeating vitamin B12 measurements unless lack of compliance is suspected or anemia recurs"	"Emphasize the importance of attempting to assess whether deficiency is present before requesting vitamin B12 levels ... assess medication, family history, diet, alcohol intake and symptoms of malabsorption"
Andres et al, 2004 (4)	All elderly who are malnourished All patients in institutions and psychiatric hospitals All patients with hematological or neuropsychiatric manifestations of vitamin B12 deficiency	Not reported	Not reported

Conclusions

- The volume of vitamin B12 tests increased substantially in Ontario when the vitamin B12 test was added to the laboratory requisition form in 2007.
- The serum vitamin B12 test has low diagnostic accuracy.
- Three guidelines on diagnosing vitamin B12 deficiency were identified, with limited evidence supporting the recommendations.
- Patients with symptoms or signs of vitamin B12 deficiency anemia (macrocytic anemia) should be tested for vitamin B12 deficiency. It is unclear whether other special populations should be tested for B12 deficiency (e.g., patients with suspect neuropsychiatric abnormalities).
- The frequency with which patients should be tested is unclear.

Acknowledgements

Editorial Staff
Pierre Lachaine
Jeanne McKane, CPE, ELS(D)

Medical Information Services
Kellee Kaulback, BA(H), MISt

Appendices

Appendix 1: Literature Search Strategies

Search date: June 28, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Wiley Cochrane; Centre for Reviews and Dissemination (CRD) database

---

1 exp Vitamin B 12 Deficiency/ use mesz (9232)
2 exp cyanocobalamin deficiency/ use emez (5986)
3 exp Vitamin B 12/ or exp Transcobalamins/ use mesz (45211)
4 exp transcobalamin/ or exp cyanocobalamin/ use emez (27433)
5 exp iron deficiency/ or exp iron blood level/ or exp iron overload/ use emez (19132)
6 exp Anemia/ (348498)
7 exp Hemochromatosis/ (16760)
8 exp Transferrins/ use mesz (19258)
9 exp transferrin/ use emez (20499)
10 exp ferritin/ or exp ferritin blood level/ use emez (39716)
11 exp Ferritins/ use mesz (15449)
12 exp Iron/ (167137)
13 iron overload.ti,ab. (13797)
14 (iron or hemochromatos* or ferritin* or cyanocobalamin* or transferrin* or b12 or b 12 or cobalamin* or transcobalamin* or holotranscobalamin* or holotc).ti,ab. (354035)
15 (an?emia* adj2 (b12 or b 12 or addison* or pernicious* or iron)).ti,ab. (22662)
16 or/1-15 (735822)
17 exp "Sensitivity and Specificity"/ (530170)
18 exp "Reproducibility of Results"/ use mesz (234104)
19 exp reproducibility/ use emez (127766)
20 exp "Predictive Value of Tests"/ use mesz (121365)
21 exp predictive value/ use emez (17963)
22 exp diagnostic accuracy/ use emez (160996)
23 exp Diagnostic Tests, Routine/ use mesz (6027)
24 exp Mass Screening/ use mesz (91380)
25 exp Screening/ use emez (368360)
26 exp Clinical Laboratory Techniques/ use mesz (1972392)
27 exp laboratory test/ use emez (100291)
28 exp Vitamin B 12 Deficiency/bl, co, di [Blood, Complications, Diagnosis] (4427)
29 exp cyanocobalamin deficiency/co, di [Complication, Diagnosis] (2061)
30 exp Anemia/bl, co, di [Blood, Complications, Diagnosis] (53169)
31 exp Hemochromatosis/bl, co, di [Blood, Complications, Diagnosis] (3207)
32 exp Hematologic Tests/ use mesz (196319)
33 exp blood analysis/ use emez (102122)
34 (sensitivity or specificity or screen* or diagnos* or ppv or NPV or accuracy or clinical utility or predictive).ti,ab. (5465651)
35 exp Ferritins/bl, df, du, st [Blood, Deficiency, Diagnostic Use, Standards] (7435)
36 exp Vitamin B 12/bl, du, st [Blood, Diagnostic Use, Standards] (4628)
37 exp Transferrin/bl, df, du, st [Blood, Deficiency, Diagnostic Use, Standards] (617)
38 exp Risk Factors/ or exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ use mesz (2398139)
39 exp Risk Factor/ or Cancer Risk/ or exp cross-sectional study/ or exp cohort analysis/ or exp case control study/ use emez (2442326)
40 or/17-39 (9540406)
41 ((elevated or raised or inadequa* or deficien* or insufficien* or high blood level* or high serum level* or high plasma level* or low blood level* or low serum level* or low plasma level* or suboptimal or sub-optimal or subnormal or sub-normal) adj (iron or ferritin* or cyanocobalamin* or transferrin* or b12 or b 12 or cobalamin* or transcobalamin* or holotranscobalamin* or holotc)).ti,ab. (3680)
42 40 or 41 (9541738)
43 exp Technology Assessment, Biomedical/ use mesz (8702)
44 exp Biomedical Technology Assessment/ use emez (11295)
45 exp meta analysis/ use emez (63777)
46 exp Meta-Analysis/ use mesz (34386)
47 ((health technolog* or biomedical technolog*) adj2 assess*).mp. (14204)
48 (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (324750)
49 or/43-48 (345143)
50 16 and 42 and 49 (2630)
51 limit 50 to english language (2453)

52 limit 51 to yr="2000 -Current" (2220)
53 remove duplicates from 52 (1860)

References

(1) Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency. Arch Int Med. 1999;159(6):1289-98.

(2) McLean E, de Benoist B, Allen LH. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull. 2008;29(2):S38-S51.

(3) Allen LH. How common is vitamin B12 deficiency? Am J Clin Nutr. 2009;89(suppl):693S-6S.

(4) Andres E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. Can Med Assoc J. 2004;171(3):251-9.

(5) Tucker KL, Rich S, Rosenberg I, Jacques P, Dallal G, Wilson PWF, et al. Plasma vitamin B12 concentrations relate to intake source in the Framingham Offspring Study. Am J Clin Nutr. 2000;71(2):514-22.

(6) Willis CD, Elshaug AG, Milverton JL, Watt AM, Metz MP, Hiller JE. Diagnostic performance of serum cobalamin tests: A systematic review and meta-analysis. Pathol. 2011;43(5):472-81.

(7) Hvas A-M, Nexo E. Diagnosis and treatment of vitamin B12 deficiency. An update. Haematologica. 2006;91(11):1506-12.

(8) BC Guidelines and Protocols Advisory Committee. Cognitive impairment in the elderly: recognition, diagnosis and management. British Columbia: BC Ministry of Health. 2007 [cited 2012 Aug 28]. 4 p. Available from: http://www.bcguidelines.ca/guideline_cognitive.html

(9) Pitner JK, Bachman DL. A synopsis of the practice parameters on dementia from the American Academy of Neurology on the diagnosis of dementia. Consult Pharm. 2004;19(1):52-63.

(10) Kulnigg S, Gasche C. Systematic review: Managing anaemia in Crohn's disease. Aliment Pharm Ther. 2006;24(11-12):1507-23.

(11) BC Guidelines and Protocols Advisory Committee. Cobalamin (vitamin B12) deficiency: investigation and management. British Columbia: BC Ministry of Health. 2012 [cited 2012 Aug 28]. 4 p. Available from: http://www.bcguidelines.ca/guideline_cobalamin.html

(12) Smellie WSA, Wilson D, McNulty CAM, Galloway MJ, Spickett GA, Finnigan DI, et al. Best practice in primary care pathology: Review 1. J Clin Pathol. 2005;58(10):1016-24.

(13) AGREE Working Group. Appraisal of guidelines for research and evaluation II (AGREE). Hamilton (ON): AGREE Working Group. 2009 [cited 2012 Aug 28]. 56 p. Available from: http://www.agreetrust.org/

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca