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Ferritin Testing: A Rapid Review

Health Quality Ontario

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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 This rapid review may be superseded by an updated publication on the same topic.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

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Table of Contents

List of Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
CHF	Congestive heart failure
IDA	Iron deficiency anemia
OAML	Ontario Association of Medical Laboratories
USPSTF	United States Preventative Services Task Force

Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Objective of Analysis

The objective of this rapid review is to establish who should be assessed for iron deficiency or iron overload.

Clinical Need and Target Population

Iron Deficiency

Iron deficiency anemia (IDA) occurs when the loss of iron exceeds the body's ability to absorb dietary iron and iron stores are depleted such that there is insufficient to maintain healthy red blood cells. The prevalence of IDA varies by age and gender. In premenopausal women aged 20 to 49 years the prevalence of IDA is 11%, whereas in men aged over 50 years it is about 2% to 4%. (1)

Causes of iron loss include gastrointestinal conditions such as peptic ulcers, cancer, inflammatory bowel disease, and gastritis. Increased iron loss can also occur in people with urinary blood loss or who donate blood frequently or in women with menorrhagia. Patients with malabsorption conditions such as celiac disease are also at a higher risk of IDA. Adolescents and pregnant women also have a higher demand for iron. (1)

Iron Overload

There are 2 forms of iron overload (hemochromatosis): the first is an inherited form in which the digestive tract absorbs too much iron; the second form occurs due to blood-related disorders (e.g., thalassemia) or in patients who receive many blood transfusions. Alcoholism is also associated with an increased risk of iron overload. (2) A study by Krikler and Heathcote (3) estimated the prevalence of iron overload to be 3 or 4 per 1,000 in men living in British Columbia.

Technique

In 1992, Guyatt et al (4) published a systematic review comparing the laboratory tests used to diagnose IDA. Their review included results from 55 studies comparing ferritin, transferrin saturation, mean cell volume, and red cell volume distribution. They found the lab test for ferritin to be the most sensitive and specific test for the diagnosis of IDA in the general population.

Ontario Context

Fiscal year 2010/2011 saw approximately 3.5 million ferritin laboratory tests billed to the province at a cost of approximately $36 million (Table 1), far more than any of the other iron assessment tests. It is important to note that according to the schedule of laboratory fees issued by the Ministry of Health and Long Term Care (5) (http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/labfimm.html, accessed August 24, 2012) the laboratory test for total iron binding capacity cannot be claimed at the same time as a ferritin test.

Table 1: Iron Laboratory Tests Performed in Ontario in Fiscal Year 2010/2011

Laboratory Test	Community Tests, n	Hospital Tests, n	Cost, $
Ferritin	3.1 million	400,000	36 million
Transferrin saturation	9,000	60,000	57,000 (community only)
Total iron with iron-binding capacity and percent saturation	125,000	248,000	5.6 million
Iron-binding capacity	15	0	127

The number of ferritin tests performed since fiscal year 2005/2006 has increased, particularly in the community setting (Table 2, Figure 1). Of note, in August 2007 the ferritin test was added to the laboratory requisition form that physicians use to request lab tests, and the number of tests for ferritin increased by nearly 1 million between 2007 and 2008.

Table 2: Number of Ferritin Laboratory Tests Performed in Ontario from Fiscal Year 2005/2006 to 2010/2011

Fiscal Year	Community Tests, n	Hospital Tests, n	Total
2005/2006	1,422,120	282,963	1,705,083
2006/2007	1,535,426	315,288	1,850,714
2007/2008	1,858,535	336,667	2,195,202
2008/2009	2,763,375	372,343	3,135,718
2009/2010	3,186,199	445,952	3,632,151
2010/2011	3,086,475	397,252	3,483,727

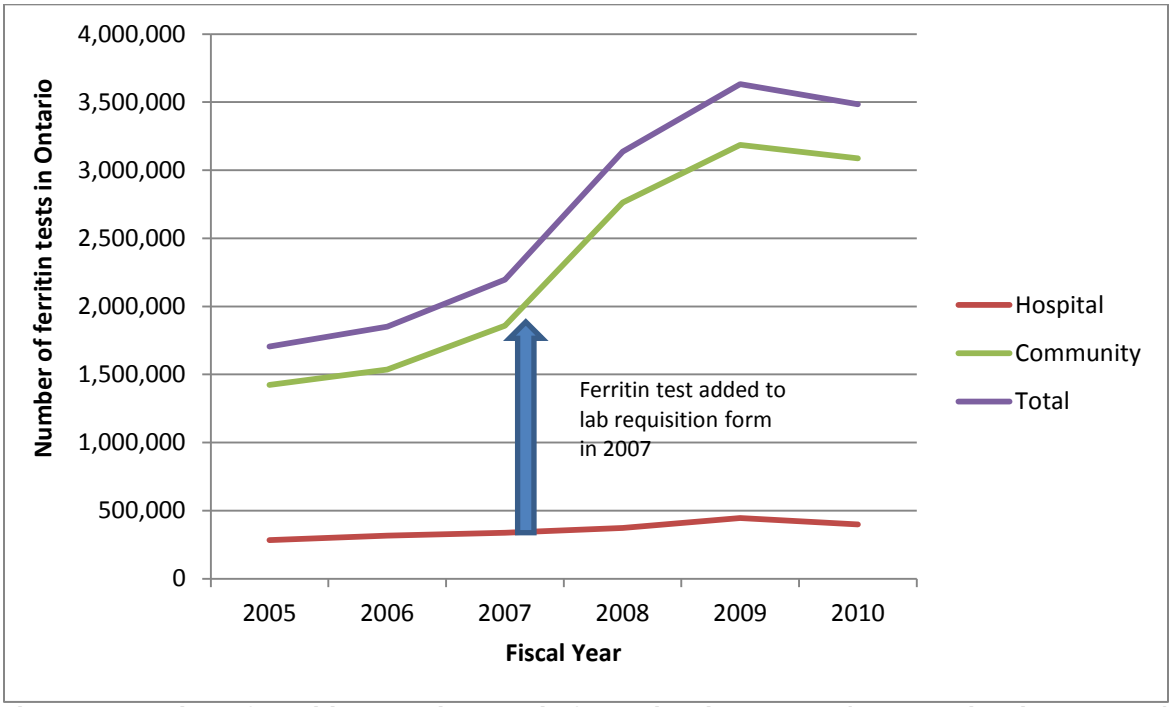

Figure 1: Number of Ferritin Tests in Ontario from Fiscal Year 2005/2006 to Fiscal Year 2010/2011

Rapid Review

Research Question

Who should be tested for iron deficiency or iron overload?

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 full-text reports
- published between January 1, 2000, and June 28, 2012
- systematic reviews, meta-analyses, clinical practice guidelines

Exclusion Criteria

- studies investigating the treatment of or interventions for the management of iron deficiency or iron overload
- randomized controlled trials, observational studies, case series, editorials

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.

No systematic reviews assessing the clinical utility of ferritin testing were identified. However, several guidelines and non-systematic reviews on the diagnosis of iron deficiency anemia (IDA) and iron overload were found. Table 3 lists the 4 different guidelines (6-9) and their recommendations.

Table 3: Guidelines for the Assessment of Iron Deficiency or Iron Overload

Guideline	Recommendations	Evidence
OAML, 2012 (6)	Screening of the general population is not indicated At-risk populations with clinical signs and symptoms and patients with microcytic anemia should be considered for screening	No systematic review No link to evidence
BC Guidelines & Protocols Advisory Committee, 2010 (iron deficiency) (9)	Screening of the general population for iron deficiency is not recommended Identify patients at risk of iron deficiency based upon a directed history, symptom review, and physical examination	Recommendation is based on the USPSTF's 2006 recommendation, which specifically targeted children and pregnant women and not the general population
USPSTF, 2006 (7)	The evidence is insufficient to recommend for or against routine screening IDA in asymptomatic children aged 6 to 12 months The USPSTF recommends routine screening for IDA in asymptomatic pregnant women	The USPSTF found at least fair evidence that screening improves important health outcomes and concludes that benefits outweigh harms
BC Guidelines & Protocols Advisory Committee, 2006 (iron overload) (8)	Patients who have symptoms or signs that might be caused by iron overload should be tested. This includes patients with unexplained • arthritis • CHF • adult-onset diabetes • persistent elevation of liver enzymes or cirrhosis • secondary hypogonadism • increased skin pigmentation and patients with persistently elevated serum ferritin not explained by an underlying inflammatory systemic disease	No systematic review No link to evidence

Abbreviations: BC, British Columbia; CHF, congestive heart failure; IDA, iron deficiency anemia; OAML, Ontario Association of Medical Laboratories; USPSTF, United States Preventative Services Task Force.

The guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) scoring tool (Table 3). (10) Only the guideline commissioned by the United States Preventative Services Task Force (USPSTF) provided the evidence on which the recommendations were based. (7) The British Columbia Guidelines & Protocols Advisory Committee guideline on iron deficiency (9) did not provide its own evidence base but cited the USPSTF guideline. However, the USPSTF guideline (7) specifically targeted children and pregnant women, whereas the BC guideline (9) was aimed at the general population, which was beyond the scope of the USPSTF guideline.

Table 4: AGREE Appraisal Summary for Each Iron Testing Guideline

Guideline	Scope and Purpose (out of a total of 21)	Stakeholder Involvement (out of a total of 21)	Rigour of Development (out of a total of 56)	Clarity of Presentation (out of a total of 21)	Applicability (out of a total of 28)	Editorial Independence (out of a total of 14)
OAML, 2012 (6)	15	15	12	15	7	4
BC Guidelines & Protocols Advisory Committee, 2010 (iron deficiency)(9)	15	9	13	19	4	5
USPSTF, 2006 (7)	21	14	51	19	13	7
BC Guidelines & Protocols Advisory Committee, 2006 (iron overload) (8)	17	13	14	20	9	5

Abbreviations: AGREE, Appraisal of Guidelines for Research and Evaluation; BC, British Columbia; OAML, Ontario Association of Medical Laboratories; USPSTF, United States Preventative Services Task Force.

Conclusions

- The volume of ferritin tests increased substantially in Ontario when the ferritin test was added to the laboratory requisition form in 2007.
- The ferritin test is more accurate in diagnosing iron deficiency anemia (IDA) in the general population than the other available tests.
- Based on evidence from the United States Preventative Services Task Force (USPSTF), asymptomatic pregnant women should be screened for IDA, as this is associated with prematurity and low birth weight in pregnancy.
- Based on expert opinion, the ferritin test should be limited to cases of unexplained anemia, asymptomatic pregnant women, cases of suspected iron overload, or cases of chronic blood loss.

Acknowledgements

Editorial Staff
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Appendix

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

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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)

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(8) Guidelines and Protocols Advisory Committee. Iron overload--investigation and management [Internet]. Vancouver (BC): Ministry of Health; 2006 Dec 15 [cited 2012 Aug 28]. 6 p. Available from: http://www.bcguidelines.ca/guideline_iron_overload.html

(9) Guidelines and Protocols Advisory Committee. Iron deficiency--investigation and management [Internet]. Vancouver (BC): Ministry of Health; 2010 Mar 15 [cited 2012 Aug 28]. 6 p. Available from: http://www.bcguidelines.ca/guideline_iron_deficiency.html

(10) AGREE Working Group. Appraisal of guidelines for research and evaluation II (AGREE) [Internet]. 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