



Centre for Clinical Effectiveness

Enhancing patient outcomes through clinical application of the best available evidence

EVIDENCE CENTRE
CRITICAL APPRAISAL
Series 2003: Diagnosis

Diagnosing iron deficiency in patients with chronic renal failure.

Tari Turner

Southern Health

MONASH
UNIVERSITY

Centre for Clinical Effectiveness
Monash Institute of Health Services Research
Monash Medical Centre
Locked Bag 29
Clayton VIC 3168
Australia

Telephone: +61 3 9594 7505
Fax: +61 3 9594 7552
Email: cce@med.monash.edu.au (quote author of report)
URL: <http://www.med.monash.edu.au/healthservices/cce/>

September 2003

SUMMARY STATEMENT

Disclaimer - please refer to Appendix 1 for information.

Copyright – please refer to Appendix 1 for information.

Publication of materials – please use the following format when citing this article:

Turner, T. 2003 Diagnosing iron deficiency in patients with chronic renal failure. (The Centre for Clinical Effectiveness), Available:
<http://www.med.monash.edu.au/healthservices/cce>

[Accessed:Access date...]

Form Version – B.2002.01.05.1

REQUEST

Which test or combination of tests are most accurate in diagnosing iron deficiency in patients with chronic renal failure?

REQUESTED BY

Dr Amanda Walker, Director, Paediatric Renal and Continence Service, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias.

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments. Then we identify diagnostic studies with independent blind comparison of an appropriate spectrum of consecutive patients, who have undergone both the diagnostic test and the reference standard. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable, or have other methodologic difficulties. While we cite observational and case series studies, narrative reviews and consensus statements in our reports, we do not critically appraise them. These studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request

Patients (Subject): Patients with chronic renal failure
Diagnostic test: Serum ferritin, total iron-binding capacity, transferrin saturation, erythrocyte ferritin, serum transferrin receptor
Reference test: Bone marrow examination*
Diagnosis: Iron deficiency

*Bone marrow examination was chosen as the appropriate reference test in consultation with the requesting clinician, and is supported by the literature. There is some discussion in the literature as to whether response to iron therapy might be a more appropriate standard, however this is beyond the scope of this report.

Search terms

(see Appendix 2 for exact search strategy)

Patient (Subject): chronic renal failure, chronic kidney failure, chronic disease
Diagnosis: iron deficiency, anaemia

Resources Searched

We searched the following databases and internet websites:

Resource	Issue or Access Date
Australasian Medical Index	August 14, 2003
Biological Abstracts (OVID)	1980 to June 2003
CINAHL (OVID)	1982 to August Week 2 2003
The Cochrane Library (Online)	Issue 3, 2003
EBM Reviews (OVID) -	
Cochrane Database of Systematic Reviews	2nd Quarter, 2003
Database of Abstracts of Reviews of Effectiveness	2nd Quarter, 2003
Cochrane Controlled Trials Register	2nd Quarter, 2003
Medline (OVID)	1966 to August Week 1, 2003
National Guideline Clearinghouse (Online)	August 14, 2003
PREMEDLINE (OVID)	August 13, 2003

Refinements, Searching & Reporting Constraints

We applied the following inclusion and exclusion criteria:

Inclusion Criteria

- Primary studies comparing the accuracy with which tests diagnose iron deficiency in patients with chronic renal failure compared to the reference standard of bone marrow examination (or systematic reviews of these studies)

Exclusion Criteria

- Studies including patients without chronic renal failure
- Studies examining less than five patients
- Studies published in a language other than English
- Studies presenting data included in another published report

RESULTS:

From our sources we identified 16 potentially relevant articles. We obtained the full text of these articles to determine their relevance.

After examination of the 16 articles, the following were excluded as follows:

Reason for exclusion	Number
Appropriate reference standard not used	9
Patient population includes patients without chronic renal failure	1
Narrative review or editorial	4
Total	14

2 articles then remained for appraisal. These studies are classified as follows:

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised Controlled Trial	0
Diagnostic cross sectional study	2
Total	2

Based on our refinements, searching and reporting constraints we are reasonably confident these articles represent the most relevant findings published to date.

BRIEF SUMMARY OF RESULTS OF APPRAISAL

The evidence identified regarding diagnosis of iron deficiency in patients with chronic renal failure does not provide a clear answer to the question posed.

The two studies of appropriate design identified were both small and included diverse patient groups. The diagnostic approaches employed in these two trials were slightly different, making comparison of their results difficult.

Different approaches to interpreting the results of the bone marrow examination, used as the reference test in these trials, further complicates analysis of their results.

EVIDENCE SUMMARIES

	Study 1	Study 2
	Fernandez-Rodriguez AM, Guindeo-Casasus MC, Molero-Labarta T et al, 1999. 'Diagnosis of iron deficiency in chronic renal failure'. American Journal of Kidney Diseases 34 (3) 508-13.	Kalantar-Zadeh K, Hoffken B, Wunsch H, Fink H, Kleiner M & Luft FC, 1995. 'Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era.' American Journal of Kidney Diseases 26 (2) 292-9. [Corrected figures in 27 (5) 762-4]
STUDY DESIGN	Level I: Diagnostic Cross Sectional Study	Level I: Diagnostic Cross Sectional Study
DESCRIPTION: Patients (subjects), Diagnostic Test, Comparison, Outcomes	<p>Patients (subjects): 63 patients (47 men, 16 women) undergoing regular haemodialysis (n=29) or continuous ambulatory peritoneal dialysis (n=34) between June 1994 and December 1995. Ages ranged from 23 to 79 years, mean=57.3 years. 30 patients had type 2 diabetes mellitus.</p> <p>Diagnostic tests: Haemoglobin concentration, haematocrit, serum albumin and transferrin, serum iron and total iron-binding capacity, transferrin saturation index and serum ferritin.</p> <p>Comparison: Bone marrow examination. Slides were graded; 0 no iron, +1 slight amount of iron or patchy iron stores, +2 diffuse iron staining, and +3 extensive iron staining (iron overload). Normal values were considered to be +1 or +2 on this scale.</p> <p>Outcome: Iron deficiency.</p> <p>Inclusion/Exclusion Criteria: For inclusion, patients had to be clinically stable, and not have received IV iron therapy or rHuEPO within 3 months previous to the study. Patients with hepatocellular damage, malignancy, or infections known to alter serum ferritin and serum transferrin receptor levels were excluded, as were patients with episodes of peritonitis, access graft infection or other intercurrent process within two months prior to study commencement.</p>	<p>Patients (subjects): 25 patients with chronic renal failure (13 men and 12 women) aged between 44 and 84 years. All patients had creatinine concentration >3mg/dL for at least three months and had a normochromic normocytic anaemia with haemoglobin less than 11g/dL. 16 patients were on haemodialysis, and 4 on continuous ambulatory peritoneal dialysis. 2 patients had poorly functioning renal allografts. 23 patients had received EPO and 2 were not being treated with EPO. Iron therapy was withdrawn from those patients receiving it between 13 and 30 days prior to the study.</p> <p>Diagnostic test: Haemoglobin, serum ferritin, serum transferrin, serum iron, total iron binding capacity (=serum transferrin (mg/dL) x 1.25), transferrin saturation index (serum iron/total iron binding capacity).</p> <p>Comparison: Bone marrow examination. Slides were graded; 0-no iron, +1 slight amount of iron, +2 patchy iron stores, +3 patchy to diffuse staining, +4 diffuse iron staining, and +5 extensive iron staining (iron overload). Normal values were considered to be +3 or +4 on this scale.</p> <p>Outcome: Iron deficiency.</p> <p>Inclusion/Exclusion Criteria: Not stated.</p>
VALIDITY: Methodology, rigour, selection	<p>Reference test (Gold standard): Appropriate reference test (bone marrow examination) was applied, however the statistical analyses provided do not compare the tests ability to distinguish between those patients with iron deficiency (bone marrow value: 0) and those without (+1, +2 and +3), but rather between those patients with iron deficiency (0) and those with high iron levels (+2) or iron overload (+3).</p> <p>Patient spectrum: Small and diverse but appropriate spectrum.</p>	<p>Reference test (Gold standard): Appropriate reference test (bone marrow examination) was applied in all patients.</p> <p>Patient spectrum: Very small and diverse but appropriate spectrum.</p> <p>All patients tested with reference test: Yes</p> <p>Blinding of assessors: Iron status on bone examination determined by haematologist blinded to patient information</p>

	<p>All patients tested with reference test: Yes. Blinding of assessors: Iron status on bone examination determined by haematologist blinded to patient information including haematologic values.</p>	<p>including haematologic values.</p>																																																						
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Bone marrow scores of 0 (no iron) were obtained in 16 patients, +1 (minimal iron) in 21 patients, +2 (extensive iron) in 22 patients, and +3 (iron overload) in 4 patients.</p> <p>There were no statistically significant differences in bone marrow results in relation to sex, age, presence of diabetes, type of dialysis and time on dialysis.</p> <p>There were no statistically significant differences between bone marrow result groups in relation to haemoglobin concentration, haematocrit, serum albumin, serum iron, total iron-binding capacity or transferrin saturation index.</p> <p>Serum and erythrocyte ferritin concentrations were significantly lower in patients with bone marrow scores of 0 compared with patients with scores of +2 or +3 (serum ferritin $p < 0.01$, erythrocyte ferritin $p < 0.05$) but not compared to those patients with scores of +1.</p> <p>Serum transferrin receptor values were significantly higher in patients with bone marrow scores of 0 than in those patients with scores of +2 or +3 ($p < 0.01$) but not compared to those patients with scores of +1.</p> <p>Erythrocyte ferritin and serum transferrin receptor (TFR) sensitivity and specificity values at various cut off points.</p> <table border="1" data-bbox="600 874 1319 1289"> <thead> <tr> <th rowspan="2">Specificity %</th> <th colspan="2">Erythrocyte Ferritin</th> <th colspan="2">Serum TFR</th> </tr> <tr> <th>Cut Point (ag/cell)</th> <th>Sensitivity %</th> <th>Cut Point (ug/ml)</th> <th>Sensitivity %</th> </tr> </thead> <tbody> <tr> <td>30</td> <td>57.8</td> <td>91</td> <td>1.39</td> <td>84</td> </tr> <tr> <td>40</td> <td>46.3</td> <td>85</td> <td>1.7</td> <td>78</td> </tr> <tr> <td>50</td> <td>37.6</td> <td>76.6</td> <td>1.99</td> <td>73</td> </tr> <tr> <td>60</td> <td>31.2</td> <td>66</td> <td>2.3</td> <td>67</td> </tr> <tr> <td>70</td> <td>24.5</td> <td>53.5</td> <td>2.6</td> <td>59</td> </tr> <tr> <td>75</td> <td>31.7</td> <td>46</td> <td>2.8</td> <td>55</td> </tr> <tr> <td>80</td> <td>18.9</td> <td>38</td> <td>2.9</td> <td>50</td> </tr> <tr> <td>85</td> <td>16.2</td> <td>30</td> <td>3.2</td> <td>45</td> </tr> <tr> <td>90</td> <td>13.2</td> <td>20</td> <td>3.5</td> <td>38</td> </tr> </tbody> </table>	Specificity %	Erythrocyte Ferritin		Serum TFR		Cut Point (ag/cell)	Sensitivity %	Cut Point (ug/ml)	Sensitivity %	30	57.8	91	1.39	84	40	46.3	85	1.7	78	50	37.6	76.6	1.99	73	60	31.2	66	2.3	67	70	24.5	53.5	2.6	59	75	31.7	46	2.8	55	80	18.9	38	2.9	50	85	16.2	30	3.2	45	90	13.2	20	3.5	38	<p>Bone marrow contained no iron in 3 patients (iron score 0), minimal iron in 7 patients (+1), slight to patchy iron stores in 7 patients (+2), patchy to diffuse iron stores in 13 patients (+3 or +4). No patients had iron overload on bone marrow examination.</p> <p>Scores of 0 and +1 were considered to represent absolute iron deficiency, scores of +2 were considered to represent relative iron deficiency.</p> <p>Mean haemoglobin scores were not significantly related to score on bone marrow examination.</p> <p>Serum ferritin levels were significantly lower in patients with iron scores of 0 or +1 compared with patients with iron scores of +2 or +3 or +4 ($p < 0.05$).</p> <p>Transferrin saturation values were significantly lower in patients with bone marrow iron scores of 0, +1 or +2 compared with patients with scores on +3 or +4 ($p < 0.05$).</p> <p>In diagnosing absolute iron deficiency (bone marrow score 0 or +1) serum ferritin with a cut off of < 200ng/ml was not sensitive (50%) but had a specificity of 87% and a positive predictor value (PPV) of 71%. In comparison transferrin saturation ($< 20\%$) had a sensitivity of 90% and a specificity of 40%, with a PPV of 50%.</p> <p>In diagnosing relative iron deficiency (bone marrow score 0, +1 or +2) serum ferritin with a cut off of < 200ng/ml was not sensitive (40%) but had a specificity of 100% and a positive predictor value (PPV) of 100%. In comparison transferrin saturation ($< 20\%$) had a sensitivity of 88% and a specificity of 63%, with a PPV of 83%.</p> <p>Excluding patients with serum transferrin concentrations of < 150ng/dL (i.e. correcting for hypoproteinaemia) improved the sensitivity and specificity of transferrin saturation ($< 20\%$) diagnosis of relative iron deficiency to 100% and 80% respectively, with a PPV of 94%.</p>
Specificity %	Erythrocyte Ferritin		Serum TFR																																																					
	Cut Point (ag/cell)	Sensitivity %	Cut Point (ug/ml)	Sensitivity %																																																				
30	57.8	91	1.39	84																																																				
40	46.3	85	1.7	78																																																				
50	37.6	76.6	1.99	73																																																				
60	31.2	66	2.3	67																																																				
70	24.5	53.5	2.6	59																																																				
75	31.7	46	2.8	55																																																				
80	18.9	38	2.9	50																																																				
85	16.2	30	3.2	45																																																				
90	13.2	20	3.5	38																																																				

	<p>Serum ferritin sensitivity and specificity values at various cut off points.</p> <table border="1"> <thead> <tr> <th>Serum Ferritin Cut Point (ug/L)</th> <th>Sensitivity (%)</th> <th>Specificity (%)</th> <th>Positive Predictive Value (%)</th> <th>Negative Predictive Value (%)</th> </tr> </thead> <tbody> <tr> <td>50</td> <td>50</td> <td>95</td> <td>80</td> <td>85</td> </tr> <tr> <td>100</td> <td>72</td> <td>80</td> <td>57</td> <td>90</td> </tr> <tr> <td>150</td> <td>81</td> <td>65</td> <td>45</td> <td>91</td> </tr> <tr> <td>200</td> <td>86</td> <td>55</td> <td>39</td> <td>92</td> </tr> <tr> <td>300</td> <td>92</td> <td>36</td> <td>33</td> <td>94</td> </tr> <tr> <td>600</td> <td>98</td> <td>14</td> <td>28</td> <td>100</td> </tr> </tbody> </table>	Serum Ferritin Cut Point (ug/L)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	50	50	95	80	85	100	72	80	57	90	150	81	65	45	91	200	86	55	39	92	300	92	36	33	94	600	98	14	28	100	
Serum Ferritin Cut Point (ug/L)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)																																	
50	50	95	80	85																																	
100	72	80	57	90																																	
150	81	65	45	91																																	
200	86	55	39	92																																	
300	92	36	33	94																																	
600	98	14	28	100																																	
<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>"Serum ferritin concentration was the most reliable parameter for the detection of deplete iron stores"</p> <p>"When sensitivity, specificity, and positive and negative predictive values are considered together, serum ferritin values greater than 100ug/l could be useful to exclude iron deficiency, with a sensitivity and specificity of 75% for a cut off point of 121ug/L."</p> <p>"Although it has been reported that in anemic patients, serum transferrin receptor is a valuable tool for the diagnosis of anemia of chronic disease, in our study of stable chronic renal failure patients undergoing dialysis, this parameter was not superior to serum ferritin in the diagnosis of iron depletion."</p>	<p>"Although serum ferritin concentration increased with increasing iron stores in our patients, the scatter in the data shown in the figure was such that for any given patient, the predictive value of the diagnosis was minimal."</p> <p>"the transferrin saturation had a sensitivity of almost 90%, which makes that test a much more reliable marker in terms on identifying candidates for iron deficiency anemia. The specificity of 63% is not ideal, nonetheless, the test meets the criterion of an adequate screening test for the diagnosis."</p> <p>"On the basis of our findings we recommend both measurements of serum ferritin and determination of transferrin saturation. The former test offers excellent specificity, while the latter offers acceptable sensitivity. Patients with transferrin values of less than 150mg/dL should be considered separately."</p>																																			
<p>OUR COMMENTS: Opportunities for bias, weakness and strength</p>	<p>Weakness/es: Small, diverse patient group. Clinical validity of comparison between subjects with bone marrow scores of 0 and patients with scores of +2 or +3, rather than patients with scores of +1 not clear. No comparison of accuracy of diagnosis based on both serum ferritin and serum transferrin receptor levels. Strength/s: Includes multiple tests in all patients.</p>	<p>Potential for bias: Very small, diverse patient group. Weakness/es: Clinical validity of diagnosing "relative iron deficiency" as compared with "absolute iron deficiency" not clear. Strength/s: Includes multiple tests in all patients.</p>																																			

REFERENCES

ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

Fernandez-Rodriguez AM, Guindeo-Casasus MC, Molero-Labarta T et al, 1999. 'Diagnosis of iron deficiency in chronic renal failure'. *American Journal of Kidney Diseases* 34 (3) 508-13.

Kalantar-Zadeh K, Hoffken B, Wunsch H, Fink H, Kleiner M & Luft FC, 1995. 'Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era.' *American Journal of Kidney Diseases* 26 (2) 292-9. [Corrected figures in 27 (5) 762-4]

ARTICLES NOT CRITICALLY APPRAISED

Appropriate gold reference standard not used

Ahluwalia N, Skikne BS, Savin V & Chonko A, 1997. 'Markers of masked iron deficiency and effectiveness of EPO therapy in chronic renal failure'. *American Journal of Kidney Diseases* 30 (4) 532-41.

Bakkaloglu SA, Ekim M, Tumer N, Akar N & Uysal Z, 2002. 'Soluble transferrin receptor is not a reliable marker of iron deficiency in pediatric CAPD patients'. *Peritoneal Dialysis International* 22 (5) 621-5.

Baldus M, Walter H, Thies K et al, 1998. 'Transferrin receptor assay and zinc protoporphyrin as markers of iron-deficient erythropoiesis in end-stage renal disease patients'. *Clinical Nephrology* 49 (3) 186-92.

Beerenhout C, Bekers O, Kooman JP, van der Sande FM & Leunissen KM, 2002. 'A comparison between the soluble transferrin receptor, transferrin saturation and serum ferritin as markers of iron state in hemodialysis patients'. *Nephron* 92 (1) 32-5.

Matsuda A, Bessho M, Mori S et al, 2002. 'Diagnostic significance of serum soluble transferrin receptors in various anemic diseases: The first multi-institutional joint study in Japan'. *Haematologia* 32 225-38.

Taralov Z, Koumtchev E & Lyutakova Z, 1998. 'Erythrocyte ferritin levels in chronic renal failure patients'. *Folia Medica (Plovdiv)* 40 (4) 65-70.

Zupan IP, Varl J, Kovac D et al, 2001. 'Indices of iron status in patients treated by chronic haemodialysis'. *Pflugers Archiv - European Journal of Physiology* 442 (7) R202-3.

Mixed patient population

Lee EJ, Oh E-J, Park Y-J, Lee HK & Kim BK, 2002. 'Soluble transferrin receptor (sTfR), ferritin, and sTfR/log ferritin index in anemic patients with nonhematologic malignancy and chronic inflammation'. *Clinical Chemistry* 48 (7) 1118-21.

Narrative review or editorial

Brugnara C, 2002. 'A hematologic "gold standard" for iron-deficient states?' *Clinical Chemistry* 48 (7) 981-2.

Dennison HA, 1999. 'Limitations of ferritin as a marker of anemia in end stage renal disease'. *Anna Journal*. 26 (4) 409-14.

Druke TB, Barany P, Cazzola M et al, 1997. 'Management of iron deficiency in renal anemia: Guidelines for the optimal therapeutic approach in erythropoietin-treated patients'. *Clinical Nephrology* 48 (1) 1-8.

Phelps KR, 1996. 'Diagnosis of iron deficiency in dialysis patients.' American Journal of Kidney Diseases 27 (5) 762-4.

Thomas C & Thomas L, 2002. 'Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency'. Clinical Chemistry 48 (7) 1066-76.

Van Wyck DB, Bailie G & Aronoff G, 2002. 'Just the FAQs: frequently asked questions about iron and anemia in patients with chronic kidney disease'. American Journal of Kidney Diseases 39 (2) 426-32.

OTHER ARTICLES OF POSSIBLE RELEVANCE

Cameron JS, 1999. 'European best practice guidelines for the management of anaemia in patients with chronic renal failure'. Nephrology Dialysis Transplantation. 14 (SUPPL. 2) 61-65.

Macdougall IC, Horl WH, Jacobs C et al, 2000. 'European Best Practice Guidelines 6-8: Assessing and optimizing iron stores'. Nephrology Dialysis Transplantation 15 (Supplement 4) 20-32.

APPENDIX 1

Copyright

© This publication is the copyright of Southern Health. Other than for the purposes and subject to the conditions prescribed under the Copyright Act 1968 as amended, no part of this publication may, in any form or by any means (electric, mechanical, microcopying, photocopying, recording or otherwise), be reproduced, stored in a retrieval system or transmitted without prior written permission. Inquiries should be addressed to Centre for Clinical Effectiveness.

Disclaimer

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and Southern Health do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and Southern Health cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors of omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

APPENDIX 2

Levels of Evidence

The levels of evidence reflect the methodological rigour of the studies; a study assigned as level I evidence is considered the most rigorous and least susceptible to bias, while a study deemed to contain level IV evidence is considered the least rigorous and more susceptible to bias.

Evidence Regarding Diagnostic Tests

At present the National Health and Medical Research Council (NHMRC) of Australia does not have a system for assigning a hierarchy of evidence to studies of screening and diagnostic tests. The system below was developed by the Centre for Evidence Based Medicine, National Health Service Research and Development, United Kingdom (1999) and has been adapted for use here.

- | | |
|-----------|--|
| Level I | Independent blind comparison of an appropriate spectrum* of consecutive patients, all of whom have undergone both the study test and the reference standard. |
| Level II | Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the study test and the reference standard. |
| Level III | Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients. |
| Level IV | Any of: reference standard was not applied blinded or not applied independently, no reference test applied (case series). |

* An appropriate spectrum is a cohort of patients who would normally be tested for the target disorder. An inappropriate spectrum compares patients already known to have the disease with patients diagnosed with another condition, or with a separate group of normal patients (case-control).

APPENDIX 2

Search strategy

	Search terms for MEDLINE
1	Exp Anemia, Iron-Deficiency/
2	(anemia or anaemia).mp
3	Iron deficien\$.mp
4	Or/1-3
5	Exp Kidney Failure, Chronic
6	(Chronic adj2 (renal or kidney) adj2 (failure or disease)).mp
7	5 or 6
8	Diagnos\$.mp
9	4 and 7 and 8
10	limit 9 to (human and english language)

Similar terms, appropriately translated, were used in other databases.

