Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease*

Draft review available for public comment from May 21, 2012 to June 18, 2012.

Research Review Citation: Chung M, Moorthy D, Hadar N, Salvi P, Iovin RC, Lau J. Biomarkers for Assessing and Managing Iron Deficiency Anemia in Late-Stage Chronic Kidney Disease. Comparative Effectiveness Review No. 83. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-2007-10055-I.) AHRQ Publication No. 12(13)-EHC140-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Concise and well done. The key questions are presented well.	No response needed.
Peer Reviewer #2	Introduction	Very good summary of the issues at hand. Figure 1 is a superb visualization of the pathways involved in iron metabolism and related clinical measures.	Thank you. No response needed.
Peer Reviewer #3	Introduction	The introduction is adequate and describes the importance of finding and utilizing new markers to assess iron status. Indeed, current traditional markers are susceptible to interference with other concurrent physiological processes notably inflammation. Figure 1 is particularly useful in both explaining the process of iron metabolism and distribution as well as how each biomarker reflects the individual steps.	No response needed.
Peer Reviewer #4	Introduction	clearly states the current status of assessment of iron stores in the literature.	Thank you. No response needed.
Peer Reviewer #8	Introduction	The introduction is generally well written. I have a couple of observations. Page 3, lines 25-27: I disagree that inflammation doesn't affect the "newer tests." Certainly hepcidin is affected by inflammation, as is CHr, if the serum iron falls low enough. Page 3, line 31: CHr does not change as a "function of the amount of iron in the marrow." CHr falls when the transferrin sat'n falls and less iron is delivered to the developing erythron. Soluble transferrin receptor not only rises with iron deficiency but also rises as the overall size of the erythron increases (Huebers et al. Blood 75:102; 1990). Finally, I would not introduce hepcidin as a marker of iron balance. There is no agreed-upon standardized assay. Key Question #1: I think the issue of patient-centered outcomes is important, but trying to see if outcomes are affected by whether or not newer vs. older markers of iron status were used is a genuine mismatch, in my opinion.	The sentence has been revised. Now it reads “These newer markers, highlighted in yellow, are thought to be less influenced by the underlying state of inflammation in CKD” The original sentence was “The Hb content of reticulocytes (CHr) is a function of the amount of iron in the bone marrow that is available for incorporation into reticulocytes.” We believe this sentence is correct. Thank you for the information.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	In general yes I believe the strategies and criteria are well stated. Although it is unclear how only 30 studies were included (Figure 3) yet 73 references are cited in the text. It would seem that the main part of key question 4 (biologic variability) as the Fishbane (ref 70) and (Ford refs 191 and 192) are not included when discussion KQ 4.	Key Question 4 addresses the factors that may affect test performance and clinical utility of newer markers of iron status, including biological variation in diagnostic indices. Fishbane (ref 70) was included in Key Question 3 (intermediate outcomes comparing the iron management guided by the newer laboratory markers with that guided by the classical markers) and they did report coefficient of variation (CV) of CHr, TSTA and ferritin before and after IV iron treatment. However, these data do not address Key Question 4. Ford studies (refs 191 and 192 in our excluded studies list, Appendix B) did not meet one or more of the study eligibility criteria for a particular key question. These two studies were rejected because only analytic validity data were reported (so did not meet eligibility criteria for Key Question 2), and did not provide data for other Key Questions.
Peer Reviewer #2	Methods	The description of the methods is clear and appropriate for the inquiry.	No response needed.
Peer Reviewer #3	Methods	The methods utilized in this report are acceptable. Inclusion/exclusion criteria are justified and the search strategies are explicitly stated and are logical. It is well stated in this section that there exists increased heterogeneity between studies such as iron replacement and treatment with erythropoietic stimulating agents, lack of a common reference standard for assessing response to iron treatment, and the definition of baseline iron status. However, considerable heterogeneity is likely to exist between testing platforms/methods, especially around clinical sensitivity and specificity, and this should also be further elaborated in the report. Furthermore, it is unclear whether all studies included in this report are defining CKD according to the same criteria.	The testing platforms/methods were listed in the summary tables for each test comparison (in Key Question 2). We agree that considerable heterogeneity likely exists between testing platforms, and thus have added this caution to assist the interpretation of our findings. Characteristics of CKD populations for all included studies were described in Table 2.2. Most studies enrolled CKD patients on hemodialysis. Given variable baseline mean Hb, ferritin and TSAT concentrations across included studies, it appears that studies used different definitions for the CKD patients with regards to their anemia or iron status. We noted that this heterogeneity, such as the variable iron status of the study populations and background treatment across studies, further limited our ability in making comparisons across studies.
Peer Reviewer #4	Methods	Methods are justifiable and logical.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Methods	The methods seem sound (I am not a methodologist) but why would SQID results even be considered when, at my last count, there were only 3 instruments in the world?	Before we conducted the CER, clinical experts were reconvened to form the Technical Expert Panel (TEP), which served in an advisory capacity to help refine Key Questions, identify important issues, and define parameters for the review of evidence. A list of newer markers were defined a priori with input from our TEP, including CHr, %HYPO, ZPP, sTfR, hepcidin, and SQUID. We have clarified this information in "Scope of the Review" section, and the details of this process were described in "Topic Refinement and Review Protocol" section of the report.
Peer Reviewer #1	Results	The detail and tables are a bit overwhelming considering the conclusions. A lot to digest to find out there are no good answers to the key questions. Considering the outcome (which I agree with) would it not be possible to condense?	Because we did not perform meta-analysis due to large heterogeneity across studies, we feel it is important to present key information and data from individual studies using summary tables.
Peer Reviewer #2	Results	The results section is clear and, to the extent supported by the evidence, appropriately addresses the issues raised. There is a significant amount of redundancy which perhaps could be curtailed. The tables are very useful to support the literature review and to compare/contrast the methods and results of the studies involved.	Thank you. See response above.
Peer Reviewer #3	Results	The amount of detail is well described in the Tables, specifically outlining the tests assessed and their diagnostic accuracy. Furthermore, the heterogeneity surrounding IV iron and ESA treatment is well described in tabular format, thus forming the basis for future research studies.	No response needed.
Peer Reviewer #4	Results	Detail is appropriate	Thank you.
Peer Reviewer #5	Results	I think the authors have done more than an acceptable job with the presentation of the results. I can follow the tables and the figures.	Thank you. No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	As stated above refs 70, 191 and 192 certainly address biologic variability of some of these markers. Future Research is not a section that I could find. It is a table in the "Research Gaps" section. I found the table to be unwieldy and difficult to follow and would have preferred a section specifically addressing future research.	See previous responses. Briefly, Fishbane (ref 70) was included in Key Question 3 but they did not report data addressing Key Question 4.Ford studies (refs 191 and 192 in our excluded studies list, Appendix B) did not meet one or more of the study eligibility criteria for a particular key question. Table C. summarized the research gaps identified by the CER, and some suggestions for future research. A Future Research Needs project is ongoing to discuss these research gaps and to identify other research gaps related to the CET topics with input from a multidisciplinary panel of stakeholders, including patients/patient advocates, providers, private and public payers, and principal investigators/researchers.
Peer Reviewer #2	Discussion/ Conclusion	Given the lack of robustness of the data, the conclusions are appropriately muted. No important literature has been omitted. The future research section does not go far enough in charging the dialysis community with performing the needed comparable effectiveness research on CHr.	Thank you. Please also see our response above regarding future research.
Peer Reviewer #3	Discussion/ Conclusion	The findings of this report are nicely summarized in this section. It is clearly stressed that the heterogeneity across studies exists regarding high degree of heterogeneity across studies in the definitions of the reference standard (ie. response to IV iron treatment), baseline iron status of the study populations, and background treatment. Due to this heterogeneity, the authors caution the acceptance of hemoglobin content of reticulocytes and % hypochromic erythrocytes to replace traditional ferritin and TSAT albeit the low evidence. This forms the basis of not only directing future studies, but also encouraging the reassessment of current protocols for iron management.	Thank you. No response needed.
Peer Reviewer #4	Discussion/ Conclusion	The implications are that the current literature is inadequate to change our current, flawed methods of assessing iron stores. The research section reflects this.	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Discussion/ Conclusion	The implications are clear. The findings are that the key questions can't be answered because the data don't exist. Furthermore, the authors are correct in stating that it is unlikely that studies to answer the key questions will ever be done given the resources that would be required. Page ES9; lines 16-17. I would like the authors to translate what it means when they say: "there is a low level of evidence that CHr has similar or better overall test performance compared with classical markers..." What exactly is "a low level of evidence?"	No response needed. We followed the Methods Guide in evaluating the strength of the body of evidence for each Key Question with respect to four domains: risk of bias, consistency, directness, and precision. How we graded the strength of evidence for the test performance of reticulocyte hemoglobin content (CHr) comparing with that of classical markers of iron status to predict a response to IV iron treatment was described in Table 2.4. of the report. The strength of evidence pertaining to each Key Question of the CER is classified into four broad categories or grades: High, Moderate, Low, or Insufficient. We have added brief interoperation of each grade in the "Grading of Body of Executive Summary.
Peer Reviewer #1	General	A great deal of work went into this manuscript but the findings are not surprising nor that useful. They confirm what most in the field already know - namely there is not a good biomarker for monitoring iron status in CKD patients. There is little information here that will impact future practice as there is no new and helpful information. It is OK considering it says very little that is not commonly known. It needed to be done but this is a document that will be quickly scanned by those in the field and then shelved.	No response needed.
Peer Reviewer #2	General	The authors of the document did a superb job in synthesizing the existing literature and drawing the appropriate conclusions. The summary tables are particularly useful in visualizing the results and diversity of the existing studies and in supporting the text. What we are left with is that CHr and %HYPO may be superior to TSAT and serum ferritin in diagnosing iron deficiency (whatever that means operationally) but very little evidence that the uptake of the former two tests will result in any significant improvement in intermediate outcomes, safety, quality of life, morbidity/mortality or decreased costs, which is what comparative effectiveness inquiries are all about. Even if there were more compelling data	Thank you and please also see previous responses regarding future research.

Commentator & Affiliation	Section	Comment	Response
		regarding the superior effectiveness of CHr and %HYPO in guiding iron therapy, there are considerable barriers regarding their widespread adoption in the US. %HYPO is a non-starter because both LDOs and most MDOs and SDOs use central labs which entail a significant time delay between blood sample collection and analysis. The bundling of dialysis reimbursement has caused most providers to curtail lab testing, which may include CHr if the provider is charged by the lab for the test. It is my understanding that the four biggest dialysis labs, FMC/Spectra, DaVita, Satellite and Ascend all use the Bayer blood analyzer which has the CHr channel. These machines actually run a CHr on every sample but only report the result if the CHr is ordered and reimbursed. If the CHr result were routinely disclosed on the CBC report (at no additional charge), then providers would have the opportunity to use CHr on a more routine basis as a guide for iron therapy. Given this scenario, the report does not go far enough in recommending that additional well-designed, randomized prospective studies be done comparing CHr with TSAT and serum ferritin as a guide to iron therapy with outcome measures that include all of the comparative effectiveness issues raised in Key Questions 1-4. The report is clear and well-organized. The main points are clear, namely that there is low strength evidence to support the use of CHr (which is practical in the US) and %HYPO (which is not practical in the US). The conclusions are not sufficiently robust to inform practice decisions without further research. It is also premature to consider policy changes based on this report, except for the recommendation for further research mentioned above.	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	This report is clinically useful by outlining the current state of novel biomarkers of iron status (i.e. hemoglobin content of reticulocytes, % hypochromic erythrocytes, erythrocyte zinc protoporphyrin, soluble transferrin receptor, hepcidin, and SQUID). Unfortunately, clinical studies to date have not provided overwhelming evidence regarding the advantages of these novel biomarkers as compared to traditional ones when considering treatment of a patient subpopulation clearly in need of better clinical management for anemia. Furthermore, there are no apparent standard protocols for the treatment of anemia through iron replacement therapy and erythropoietic stimulating agents, thus rendering the review described herein difficult to perform. Consequently, it is uncertain whether clinicians will change their practice based on these findings. However, this report outlines specific evidence and research gaps that will hopefully be addressed in future studies. The report is well structured and the tabular descriptions were particularly helpful for summarizing the findings. The main points regarding the heterogeneity between studies are clearly stressed. This report will be particularly useful in directing future studies to cover evidence gaps by increasing the number of studies focusing on novel biomarkers of iron status as well as reassessing the effectiveness of current management strategies for iron management. Combined with the low evidence and the heterogeneity between study protocols, it is unlikely that hemoglobin content of reticulocytes and % hypochromic erythrocytes will replace traditional ferritin and TSAT measurement in the immediate future. Nevertheless, future studies aimed at reducing the research gaps hold the promise for adoption of better biomarkers for assessing iron status in patients with CKD.	Thank you. No response needed.
Peer Reviewer #4	General	The report is clinically meaningful, with appropriate key questions explicitly stated. well structured and organized	Thank you. No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	General	The major difficulty I have with this document is that the outcome was predictable. In the renal community, there is much going back and forth about iron issues - diagnosis of the various forms of iron "deficiency" (absolute or relative/functional) and the utility of the standard tests of iron status. The Europeans, and some investigators in the US, have put more effort into understanding the "newer" iron tests, such as percent hypochromic red cells ("%HYPO") and reticulocyte hemoglobin concentration. As eventually mentioned in this document, US clinics/clinicians do not have routine access to the laboratory instruments that can report these 'newer' results and so relatively few studies have been done (and very few recently) in the US using these markers. Consequently, the vast majority of US physicians are not familiar with them. Also, while the overarching goal of the project is laudable - trying to find differences between markers of iron status that will impact practice and affect outcomes in patients - coming to a meaningful conclusion is bound to be difficult, if not impossible. There are so many moving parts, including rapid swings in iron metabolism, that the small differences that might exist between various markers of iron status are swallowed by the whole. Among the confounders: co-morbidities; parenteral iron administration; dialysis for many; administration of ESAs; changing environment for reimbursement. The last, alone, will drive behaviour far more than the relative validity of any markers of iron status. The report seems to me to be well structured and well organized. The main points are clearly presented. None of the findings will inform policy or change practice.	No response needed.
Kerry Willis, PhD Senior Vice President, Scientific Activities National Kidney Foundation	General	We are pleased to have the opportunity to comment on the Draft Comparative Effectiveness Review, "Laboratory Biomarkers/or Assessing Iron Status and Managing Iron Deficiency in Late Stage Chronic Kidney Disease Patients with Anemia. " The Report is particularly timely since the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease, which covers many of the same issues, will be	Thank you for this information.

Commentator & Affiliation	Section	Comment	Response
		published this summer. We are pleased to note that there is substantial concordance with the findings of the evidence center and the new KDIGO Guideline. The KDIGO Work Group is in agreement with the AHRQ about the lack of specificity and sensitivity of the traditional tests of iron status, TSAT and ferritin, for prediction of bone marrow iron stores and erythropoietic response to iron supplementation, that there are factors, such as inflammation, that affect the biological variability of these tests, and, as a result, that there is a need for better biomarkers. In addition, the KDIGO Guideline specifically suggests: "In the absence of a clinically evident infectious or inflammatory process, assessment of CRP may suggest the presence of an occult inflammatory state that may be associated with an elevated ferritin level and ESA-hyporesponsiveness." Finally, the KDIGO Guideline notes that there are no studies that have addressed the clinical benefit, cost-effectiveness, and risk benefit comparison of using different TSAT and ferritin levels for the diagnosis of iron deficiency or as a trigger for iron supplementation. 2. We are, however, concerned that one of the goals of the Comparative Effectiveness Review appears to be reduction in the frequency of iron tests. Conversely, the KDIGO Guideline suggests: "Patients who are on ESA therapy, regardless of whether iron treatment is also being used should have tests of iron status at least every 3 months. In some circumstances, more frequent iron status testing may be appropriate, including following initiation ofESA or iron therapy or when the ESA dose or dose frequency is increased, iron status testing is also important in the assessment of patients who become less responsive to ESA treatment." There are several reasons for this recommendation: a) "In each patient there must be consideration of current and desired Hb level, ESA dose and trends in ESA dose over time, assessment of the HB response to iron supplementation, ongoing blood loss, and changes in iron status tests"	Assessment of CRP is out of scope of the current CER. Thank you for this information. I have added it to our background section. This information was described in our background section. No response needed.

Commentator & Affiliation	Section	Comment	Response
		b) The need to consider trends in iron status are highlighted by consideration of a patient with decreasing TSA T and ferritin levels which may signify the presence of gastrointestinal bleeding or excessive dialysis blood loss. As another example, an increasing TSAT and ferritin level may indicate excessive iron supplementation and a need to decrease or discontinue iron administration. Finally, an increase in ferritin level accompanied by a decrease in TSAT and Hb level suggests inflannnation-medicated reticuloendothelial blockade, c) Increasing ferritin levels in association with stable or declining TSAT levels may also indicate the presence of inflannnation, infection, or other clinical situations inducing acute phase reactants during which time the appropriateness of continued iron administration may need to be reassessed. The KDIOO Guideline recommends that serum ferritin and TSAT levels should not be measured until at least one week has elapsed since the most recent prior IV iron use. Thank you for your attention to this comparison between the Draft Comparative Effectiveness Review and the KDIGO Guideline. We hope that the final version of the Comparative Effectiveness Review will reference the KDIGO Guideline. It will be published in the Kidney International Supplement, August 15, 2012 issue, but it will also be posted online on August 1st.	We will add this reference if the final report is published after the publication of the update DKIGO Guideline.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer	General	The review is extensive and has applied rigorous methodology. The results have been stated clearly. All the sections are very well elaborated and executive summary is succinct. Congratulations on a job well done. I have a few specific comments: 1. The area of iron biomarkers, as it exists today, is grossly deficient and the current review exposes these deficiencies very well. It is clear that most of the practices are based on the experience and it is not possible to provide conclusive guidelines based on the available studies. 2. The statement in the concluding paragraph of executive summary that 'CHr may be a suitable alternative marker of iron status for guiding iron treatment and could potentially reduce the frequency of iron testing and potential harms from IV iron treatment' is rather flawed. Safety has not been shown in the studies comparing these biomarkers. Also, just because a test reduces the likelihood of iron administration and can save cost (naturally due to less iron utilization) does not mean that it is more accurate or superior in predicting response to iron administration. Without outcomes data, it is difficult to ascertain. Even if one utilizes bone marrow iron staining as a control to test the sensitivity and specificity of biomarkers in diagnosing iron deficiency, I do not believe that necessarily predicts response to iron, safety of the approach or better outcomes. 3. Please emphasize that the era when these studies were conducted was quite different as compared to the current paradigm of anemia management with different approach to hemoglobin targets or ESA use. 4. There are minor typographical errors (e.g., page ES-6, first paragraph- function iron deficiency should be functional iron deficiency).	Thank you. No response needed. We agree with safety concerns, and problems of our draft conclusion. We have revised this sentence in our conclusion, and it now reads "These results suggest that CHr may reduce potential harms from IV iron treatment through lowering the frequency of iron testing, although the evidence for the potential harms associated with testing or test-associated treatment is insufficient" We have added this information to "Applicability and Implications for Clinical and Policy Decisionmaking" section in the discussion. Corrected.
Robert Blaser	Executive Summary	1. The Renal Physicians Association (RPA) is the professional organization of nephrologists whose goals are to insure optimal care under the highest standards of medical practice for patients with renal disease and related disorders. RPA acts as the national representative for physicians engaged in the study and management of patients with renal disease. RPA supports AHRQ's very rigorous approach to comparative effectiveness	Thank you.

Commentator & Affiliation	Section	Comment	Response
		evaluation. 2. RPA agrees with AHRQ's suggested need for larger studies powered to evaluate patient centered outcomes. Currently, there are no randomized control trials of iron dosing to correct or prevent functional iron deficiency during ESA therapy driven by using /co-pairing two possible TSATs for iron deficiency. Nor is there adequate research on whether iron tests perform differently with short vs. long acting ESAs. 3. RPA recommends the report be very clear about whether any diagnostic test is to be used to predict presence or absence of bone marrow iron versus presence or absence of a clinically meaningful response to IV iron supplementation. Testing needs are different when clinical question is too much versus too little iron. One question that should be considered for future research is whether any of the tests substantially outperform ferritin in detecting tissue overload (rather than inflammation) and in predicting adverse clinical outcomes. Most of the focus in the report seems to be on detection of iron deficiency rather than overload. The latter takes on more significance with national trends to load patients with iron to reduce ESA use 4. RPA believes there is insufficient discussion of CHr results being affected depending on whether the older H3 machine or newer Advia machines are used. Cut off values of iron deficiency by CHr changed as the technique evolved over three separate machine generations; therefore earlier studies are not comparable to later ones. Further, the percentage of hypochromic red cells (%HYPO) is affected depending on how soon assays are performed after blood drawing. In the U.S. where blood samples are often shipped long distances, there may be great variability in hypochromic red cell results. It is believed that % HYPO may not an adequate test if samples cannot be delivered to a central lab within 6-8 hrs.	No response needed. Of the 27 studies were included for Key Question 2, we grouped them into two distinct categories based on the methods to operationalize a reference standard for assessing test performance: 1) a response to intravenous (IV) iron treatment; and 2) classical laboratory biomarkers, alone or in combination with each other. Studies that investigated diagnostic test is to be used to predict presence or absence of bone marrow (category 2) were summarized in Appendix D. Studies that investigated diagnostic test is to predict a response to intravenous (IV) iron treatment are the focus of Key Question 2. The question of using ferritin in detecting tissue iron overload and in predicting adverse clinical outcomes was outside of scope of current CER. We agree that considerable heterogeneity likely exists between testing platforms, and thus have added this caution to assist the interpretation of our findings. We agree with the comments on the potential issues concerning %HYPO. We mentioned the sample storage issue in "Applicability and Implications for Clinical and Policy Decisionmaking" section in the discussion section of our report.

Commentator & Affiliation	Section	Comment	Response
Jeffery Berns	General	1. Need to be very clear about whether any diagnostic test is used to predict presence or absence of bone marrow iron vs. presence or absence of a clinically meaningful response to IV iron supplementation (and how much iron to give; no data on this I am pretty sure). Since most CKD patients (and nearly all ESRD) patients don't respond to oral iron focus would be mostly on IV iron 2. Testing needs are different when clinical question is too much vs. too little iron. Do any of the tests substantially outperform ferritin in detecting tissue overload (rather than inflammation) and more importantly in predicting adverse clinical outcomes. Most of the focus seems to be on detection of iron deficiency rather than overload. The latter takes on more significance with national trends to load patients with iron to reduce ESA use 3. Do iron tests perform differently with short vs. long acting ESAs 4. Is it clinically reasonable to use iron tests to only detect excess iron and just give IV iron if tests are below some upper limit, i.e. stop using a lower limit and just give IV iron until one or more tests exceeds a threshold.	Please see responses above. The question of using ferritin in detecting tissue iron overload and in predicting adverse clinical outcomes was outside of scope of current CER. No study was identified to address this question. No response needed.