Washington State Health Care Authority

Health Technology Assessment

Autologous Blood or Platelet-Rich Plasma Injections

Draft Evidence Report: Peer Review, Public Comment & Response

April 15, 2016

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/hta/
shtap@hca.wa.gov

RESPONSES TO PEER REVIEWS AND PUBLIC COMMENTS

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

This document responds to clinical and peer reviews from the following parties:

- Alfred Gellhorn, MD (peer reviewer)
- Kimberly G. Harmon, MD (peer reviewer)
- Dr. Michael Sailer (public comment)

No other comments were received.

Specific responses pertaining to each comment are included in Table 1.

Section/ Page	Comment	Response
Alfred Gellhorn, MD (peer reviewer)		
Washington State Utilization and Cost	There appears to be no information included in the section: Washington State Utilization and Cost data.	Thank you for your comment.
Background (Page 44)	Mention is made of the lack of standardization of PRP. This is an important point that may need additional explanation – given the multitude of kits for producing PRP on the market, and the various products generated therefrom.	Thank you for your comment, we have modified the relevant statement.
Background (Page 62)	In general, the etiology of tendinopathy is not well understood. I think it is probably OK to call these a result of overuse, but there are a number of different theoretical bases for why tendinopathy develops. It may be worthwhile to point out that the lack of understanding about the physiologic basis of tendinopathy has led to the clinical situation where rational treatment options are limited.	Thank you for your comment, we have modified the relevant statement.
Background (Page 65)	It would be helpful to point out at some point in this section that conservative treatment options for degenerative tendinopathy and OA are in general quite limited and have inconclusive data for effectiveness. This is the background that provides frustration for both clinicians and patients – when patients present with one of these conditions, generally the clinician will offer NSAIDs, Tylenol, PT, steroid injection, and if these fail then proceed to surgical interventions. In the case of knee OA, the cost of a total knee replacement is very large, and if data on usage are extrapolated over the next 20 years, these costs will completely overwhelm our medical system. The search for biologic options represents a failure of mainstream conservative treatments.	Thank you for your comment, we have addressed this in the "Comparator Treatments" section in the report.
Background (Page 66)	ABI is just blood. In the mechanism of action section, it's suggested that ABI increases the concentration of platelets – not so. Additionally, the following statement is probably not correct either "platelets are the crux of PRP and ABI treatment" . ABI, since it's whole blood, doesn't try to concentrate or distill any factors from blood – more like simply creating a new injury in a chronically nonhealing location.	Thank you for your comment, we have modified the relevant sections.
Results (General)	In general the forest plots are extremely helpful for visualizing the results. After reviewing all of the results, I was impressed by the consistency of the findings that PRP outcomes are favorable especially in the intermediate and long term time periods, regardless of the condition studied.	Thank you for your comment.
Results	ABI vs PRP. Both of these approaches to treatments are	Thank you for your comment.

Section/ Page	Comment	Response
(Page 102)	biologically based, and share a theoretical framework. It's interesting to compare the differences in outcome between these approaches, but perhaps less interesting that comparing PRP against currently covered approaches that have different proposed mechanisms of action (eg steroid, Hyaluronic acid, exercise). The report also makes some comparisons between ABI and other conservative treatments (steroid, anesthetic) at various points (plantar fasciitis, elbow, Achilles eg), and so it's not completely clear whether we should be considering just PRP as the focus of the report, or ABI as a focus as well.	Both PRP and ABI are treatments of interest for the report (see key questions and inclusion/exclusion criteria in methods section).
Results (Page 195)	Cost effectiveness. The cost of PRP as well as the cost of other currently approved treamtents for tendinopathy and OA should have a larger role in the discussion. While the cost of steroid is low, the cost of other comparator treatments (HA, physical therapy, ESWT) are quite high. PRP cost varies by region and by kit, and is more or less up to the performing clinic to determine since there is no insurance coverage currently for the procedure. I am aware of PRP injections being offered at costs of $600-1500; these costs, while not insignificant, are probably less than comparator treatments that the report finds either equivalent to, or inferior to, PRP. What are the typical costs to insurance of PT 2 times a week x 6 weeks (a reasonable guess for treatment of tendinopathy or OA)? Costs for 3 HA injections twice a year? I suspect both of these would be much more expensive than an injection of PRP at average market rate.	Thank you for your comment. Unfortunately, no cost effectiveness studies met our inclusion criteria and evaluation of cost only is beyond the scope of the report.
Results (General)	It should also be noted quite strongly that throughout the results section PRP generally is superior to treatments that are currently covered, in the intermediate and long term results from the procedure. When PRP is not clearly superior, it is at least equivalent to treatments being performed. There are no data that indicate inferiority of PRP against current active treatments. While the quality of the evidence is frequently low and sometimes moderate, I get the very strong impression from the consistency of the results across various tendinopathies and OA that in the intermediate and long term, PRP is a superior treatment options when compared to pretty much all the comparitors.	Thank you for your comment. Summaries of results have been added throughout the report in order to summarize when PRP (or ABI) is superior to control treatments.
Conclusions	I don't actually see any conclusions being drawn from the synthesized data. The report goes from the results section to the strength of evidence summaries – but I wouldn't necessarily call these conclusions. I would personally conclude the following from the included strength of evidence summaries:	Thank you for your comment. Summaries of results have been added throughout the report in order to synthesize the results more succinctly. These summaries are now available in the executive

Section/ Page	Comment	Response
	PRP is superior to active control in the intermediate and long term in the treatment of elbow epicondylitis; in the long term in patellar tendinopathy; and in the short and intermediate term in rotator cuff tendinopathy PRP is superior to HA in the treatment of knee OA in terms of function and pain in the intermediate and long term; and greatly superior to a saline placebo in short and medium term pain and function. PRP is safe with a very favorable side effect profile. The magnitude of the clinical improvements in the above conditions is clinically meaningful and important, especially in the setting of limited effective conservative treatments for tendinopathy and osteoarthritis.	summary and in the results section at the beginning of each section (which were stratified by condition).
Overall Presentation of the Report	Presentation of the report – while overwhelming in its size and breadth – is very well structured and organized. The results are clear and the language is clear. This is an important document for public policy.	Thank you.
Overall Quality of the Report	Overall quality of the report is Superior (option: superior, good, fair, poor)	Thank you.
Kimberly Harmon, MD (peer reviewer)		
Executive Summary (Page 1, paragraph 2)	"PRP formulations usually contain at least a 200% increase from baseline platelet count.40" – While this is one definition some of the formulations that are included in the studies do not have that big of an increase. Arthrex ACS typically only has 1.2x baseline platelets. A better definition to encompass all PRP preparations on the market is that there is an increase of platelets over baseline.	Thank you for your comment—this has been addressed in the relevant section.
Executive Summary (Page 1, paragraph 2)	"Although the method of preparation can greatly vary, PRP preparation involves at least one high-speed centrifugation to isolate a platelet-rich buffy coat layer." Many of the current systems do not isolate the buffy coat. All of the leukocyte-poor preparations are not buffy coat systems and isolate the RBCs from plasma with platelets still suspended. These spins are usually slower and not at long as buffy-coat systems. Because of this methodology, LP-PRP is usually 1.2 – 3X baseline level of platelets while buffy coat systems increase the platelet count to 5 – 9X baseline but also typically include WBCs.	Thank you for your comment—this has been addressed in the relevant section.
Executive Summary (Page 1, paragraph 2)	"It is common to add local anesthetic to PRP and ABI to reduce pain at the injection site." It is very uncommon to add local anesthetic to PRP or ABI. This was an older technique and, at least in the US, almost nobody does this. In fact, most people, if using anesthetic at all, only	Thank you for your comment—this has been addressed in the relevant section.

Section/ Page	Comment	Response
	anesthetize the superficial tissues and not actual tendon. This is because of some research by Mazzococa that indicated the anesthetic may inhibit platelet function.	
Appraisal	The exact same 3 paragraphs [above] is repeated on page 44 under "Appraisal" and should be modified per suggestions above.	Thank you for your comment—this has been addressed.
Appraisal	• SRI question: Topic of assessment is important to address? The use of PRP and ABI in musculoskeletal conditions is common and it is important that it be addressed.	Thank you for your comment.
Appraisal	• SRI question: Public policy and clinical relevance are well defined? Yes.	Thank you for your comment.
Background (Page 62, 2.1.1 Epidemiology)	May be useful to include commonly cited fact that 30% - 50% of sports injuries are related to tendon (Kannus, 1997)	Thank you for your comment—this has been addressed in the relevant section.
Background (Page 62, 2.1.2 Tendinopathies)	It would be helpful to include more background about tendinopathies as this is where the vast majority of the studies included in the paper are. Some references/concepts to think about include the concept of tendon injury along a continuum, (Cook J, BJSM, 2009) , the fact that tendonopathy is not always activity related (Rolf 1997), and the concept of tendon pain and its relation to pathology (Rio E, Sports Med, 2014). Also the pathogenesis of tendinopathy (Liu P, Scan J Med Sci Sport, 2011).	Thank you for your comment—this has been addressed in the relevant section.
Background (Page 62, 2.1.2 Tendinopathies)	There is also significant evidence that those with diabetes are more prone to tendinopathy (Ranger TA, BJSM, 2015) and some evidence that those with lipidemia have higher rates of tendinosis. (Tilley BJ, BJSM, 2015) Tendinosis can also be caused by flouroquinolones.	Thank you for your comment—this has been addressed in the relevant section.
Background (Page 62, 2.1.2 Tendinopathies)	It should also be mentioned that treatment of tendinopathy is largely dependent on the stage on which the tendinopathy is treated with tendons that are end-stage disrepair unlikely to respond to much while other stages may respond to anything. There is no good way to clinically stage a tendon and thus most tendon studies include a heterogenous population of tendon stages and end up with about a 60% success rate (eccentric exercises, corticosteroid injections, ABI, PRP, etc).	Thank you for your comment; this has been added to the relevant section.
Background (Page 63- Achilles tendinopathy)	"Achilles tendinopathy typically results from microtears stemming from overuse of the Achilles tendon,236 although approximately 2% of cases are caused by chronic	Thank you for your comments—we have addressed them in the relevant sections.

Section/ Page	Comment	Response
	diseases such as a rheumatoid arthritis or other inflammatory joint diseases." This is probably not true. Please see above comments and literature references to the pathogenesis of tendinopathy including reference that up to 30% of severe cases of Achilles tendinopathy requiring surgery are not related to activity. (Rolf, 1997)	
Background (Page 63- Rotator cuff tendinopathy)	"Rotator cuff tendinopathy is caused by shoulder impingement, which leads to a diminished vascular supply resulting in inflammation and degeneration of the tendon.24,263 This can be related to impingement but this is only one of many causes. It is estimated that 30% of asymptomatic people over 60 have partial tears and tendinopathy of the rotator cuff. There are a multitude of factors that go into the development of tendinopathy – not just overuse.	Thank you for your comments—we have addressed them in the relevant sections.
Background (Page 63/64- Acute Local Muscle Injury)	"Diagnosed through sonography, muscle injuries are detected as areas of aberrant muscle structure with small hematomas; they may appear hyperechoic.33" Although these can be diagnosed with ultrasound, they are typically diagnosed clinically, and many people with clinically diagnosed strains will not have ultrasound findings, especially acutely.	Thank you for your comments—we have addressed them in the relevant sections.
Background (Page 64, Osteochondral Lesions of the Talus)	"Osteochondral lesions to the talus are structural injuries to the cartilage and bone on the bottom of the ankle joint.244" - bottom of the ankle joint is not a very descriptive or particularly accurate way to describe this. More accurate would be "injuries to the cartilage and bone on the superior aspect of the talus" or just "in the ankle joint"	Thank you for your comments—we have addressed them in the relevant sections.
Background (Page 64, section 2.1.4 Osteoarthritis)	More about the pathogenesis of OA is important. It is a breakdown of the articular surface of the bone which causes release of IL-1 and other cytokines causing the synovium to increase production of apoptotic cytokines. It is not inflammatory in the traditional sense of the word i.e. typically no cell mediated inflammation, but many inflammatory cytokines and chemokines. Although the pathogenesis is incompletely understood, more on current understanding would be helpful to help people understand the rationale behind the use of PRP	Thank you for your comments—we have addressed them in the relevant sections.
Background (Page 66- section 2.2 Technology)	You should add that PRP and ABI are considered minimally manipulated and therefore exempt. Current wording is a little confusing.	Thank you for your comment, we have modified the relevant section.
Background (Section 2.2.2 Injection Procedure)	"The process of obtaining PRP begins by drawing 20 to 60 mL of blood from the patient." Many commercially used kits require only 9 – 10 mL of blood. Your lower limit should be 9.	Thank you for your comment, we have modified the relevant statement.

Section/ Page	Comment	Response
	“but PRP preparation involves at least one high-speed centrifugation to separate the blood into an erythrocyte layer at the bottom, a buffy coat layer in the middle, and an acellular plasma layer at the top” – Not all PRP systems use the buffy coat, i.e. Cascade, Arthrex, Regenex, etc. In general LR-PRP systems use the buffy coat while LP-PRP systems do not.	Thank you for your comment, we have modified the relevant statement.
	“Dry needling is often done in conjunction with injections for tendinopathies and plantar fasciitis.” – dry needling (although this is a little confusing because this is most often used to mean a physical therapy technique performed with acupuncture needles) or tenotomy (more accurate in the setting of PRP or ABI) is typically either performed by a practitioner or not – it is usually not tendon dependent. Many people to PRP or ABI without dry needling/tenotomy and many people include it.	Thank you for your comment, we have modified the relevant statement.
	“If treatment is in the knee, PRP or ABI will generally be injected intra-articularly” ABI is not generally used intra-articularly as this can cause damage. Probably instead of “knee” you should rephrase this to “If treatment is for osteoarthritis, PRP will generally . . . . “ Treatment of patellar tendons, MCL, etc. are extra-articular and still about the knee.	Thank you for your comment, we have modified the relevant statement.
	“After injection, it is typically recommended that patients refrain from weight-bearing activities involving the injected joint for several days.´ Totally variable – this may be true with OA but often is not. I would say “After injection it is typically recommended that patients decrease activity for several days to several weeks”	Thank you for your comment, we have modified the relevant statement.
Background (Section 2.3.1 Dry Needling)	“Dry needling describes the process of repeatedly passing a needle through the tendon to disrupt collagen fibers and induce bleeding without injecting any substance.71,110” I would clarify that this includes a heterogenous group of treatments ranging from treatments done with small acupuncture needles by physical therapist without anesthesia to treatments performed with large bore hypodermic needles performed by physicians with local anesthetic.	Thank you for your comment, we have modified the relevant statement.
	“Needling may be ultrasound-guided and a substance such as corticosteroid or PRP may be injected after disruption of the tendon.20,110 Peppering can be done with an injectate, such as autologous blood. The needle is inserted into the tendon and a portion of the fluid is injected, then withdrawn without emerging from the skin, redirected and reinserted into the tendon for additional injection.71,132” This is all very confusing for the lay person as in the previous sentence you mention needling	Thank you for your comment, we have modified the relevant statement.

Section/ Page	Comment	Response
	and peppering with suggestion that what may be injected is different. Needling, tenotomy, dry needling, peppering are all terms that mean putting some sort of needle into the tendon. They are used somewhat interchangeably but sometimes will denote a specific technique i.e. dry needling is typically a physical therapy technique done with acupuncture needles, tenotomy is typically done with hypodermic needles by a physician, peppering and needling can also be used to denote this. You can inject something – corticosteroid, blood, or PRP after any of the techniques although typically that is only done by physicians who tend to use hypodermic needles.	
Background (Section 2.3.2 Corticosteroids)	"For the treatment of knee osteoarthritis, the American College of Rheumatology generally recommends the use of intra-articular corticosteroids.103" True but there is little evidence to support their use long term – same for tendons.	Thank you for your comment, we have modified the relevant statement.
Background (Section 2.3.4 Hyaluronic Acid)	More should be included on this modality as it is the major comparator in most OA studies. As you know, recently the AAOS recommended against the use of HA in OA based on doubtful evidence of clinical benefit, while other societies disagree with this analysis (American College of Rheumatology, American Medical Society for Sports Medicine). It is considered a standard treatment for OA in European and Asian countries.	Thank you for your comment, we have added more detail regarding HA as a comparator treatment.
Background (Section 2.3.6 Exercise, section 2.3.7 ESWT, section 2.3.8 Low level laser therapy)	You have made statements regarding the effectiveness of these treatments and reference appropriately, however, there is much debate on whether many of these things – eccentric exercises, ESWT which is heterogeneous in how it is applied and used, and laser therapy work. I'm concerned that when there are statements about how these things work that are not held up to the same rigorous standards that you later hold up PRP and ABI that this may lead to erroneous interpretation of the evidence.	Thank you for your comment, we have modified the relevant sections.
Background (Section 2.3.10 Surgery)	"Surgery is usually the last option for tendinopathy treatment, as failure rates for debridement and/or decompression are has high as 20% to 30%.9" Failure rates in some studies are as high as 50% for tendon surgery – can't remember reference – recently did lit search on this	Thank you for your comment.
Objectives and Key Questions	• SRI question: Aims/objectives clearly address relevant policy and clinical issue? The objectives and aims are clearly stated. • SRI question: Key questions clearly defined and	Thank you.

Section/ Page	Comment	Response
	adequate for achieving aims? Yes.	
Methods	• SRI question: Method for identifying relevant studies is adequate? Yes • SRI question: Criteria for the inclusion and exclusion of studies is appropriate? Yes • SRI question: Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes	Thank you.
Methods	• SRI question: Data abstraction and analysis/review are adequate? Yes, although some of the subtleties in different studies are lost. I don't think you can include dry needling and corticosteroid injection in the same group. These are completely different treatments. I would compare separately to dry needling, corticosteroid injection or saline injection.	Thank you for your comment. As stated in the methods, based on clinical expert input prior to conducting the data analysis, it was appropriate to combine data for conservative control treatments for tendinopathies and plantar fasciitis in order to facilitate understanding the comparative impact of PRP (or ABI) compared with conservative control treatments. However, across all outcomes, subgroup analysis was performed to assess for potential heterogeneity due to differences in control treatment. If results varied by any subgroup assessed, results were stratified by that subgroup (e.g., use of steroid vs. anesthetic injection in the control group). That said, we went back through the results sections in which data were combined for dry needling and other conservative control therapies to make sure pooling of data (qualitatively or quantitatively) was appropriate-that is, that there was no heterogeneity in conclusions based on the control treatment. We noted a few instances where

Section/ Page	Comment	Response
		outcomes needed to be separated by control group and have done so for the following: • Achilles tendinopathy (ABI vs. control), section 4.1.3.2, differences in short-term function results noted for ABI vs. DN and ABI vs. exercise: SoE conclusions had been presented together for ABI vs. DN and ABI vs. exercise and have now been separated due to differing conclusions • Patellar tendinopathy (PRP vs. control), section 4.1.4.1, differences in intermediate-term function results noted for PRP + DN vs. DN and PRP vs. ESWT: Results section and SoE conclusions had been presented together for PRP + DN vs. DN and PRP vs. ESWT; both have now been separated due to differing conclusions • Patellar tendinopathy (PRP vs. control), section 4.1.4.1, differences in intermediate-term pain results noted for PRP + DN vs. DN and PRP vs. ESWT: SoE conclusions had been presented together for PRP + DN vs. DN and PRP vs. ESWT and have now been separated due to differing conclusions
Results	• SRI question: Amount of detail presented in the results section appropriate? Yes, but there is no real synthesis for results. There are 80 pages of results but it is really hard to make anything of all these results without any clinical context. Hard,	Thank you for your comments. Summaries of results have been added throughout the report in order to synthesize the results more succinctly. These summaries are now available in the executive

Section/ Page	Comment	Response
	especially for someone without a great deal of clinical knowledge to understand the results presented in this format.	summary and in the results section at the beginning of each section (which were stratified by condition).
	• SRI question: Key questions are answered? Not really. The key questions are listed below. There are 80 pages of results with no conclusions to answer the questions below. I think you need to restate the questions, give concise summary answers in a "Conclusions" section.	
	Key question 1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo? *Should there be a statement like "the evidence is limited by the heterogeneity of the study population, methods and comparators, in general it seems that there is a low degree of evidence that ABI/PRP is effective in intermediate and long-term pain and function in elbow epicondylitis compared to . . . . " or a more concise, readable summary table is needed.*	
Results	Key question 2. What is the evidence regarding short- and long-term harms and complications of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo? *This requires a summary statement.*	
Results	• SRI question: Figures, tables and appendices clear and easy to read? Yes – but need a summary figure that is concise and easy to read	
Results	• SRI question: Implications of the major findings clearly stated? Basically – no evidence see comments above.	
Conclusions	• SRI question: Are the conclusions reached valid? There are no conclusions – a "conclusions" section is not outlined in the table and I could not find any conclusions other than individual results of different comparators. See discussion above in results section.	
Overall/ general	• SRI question: Is the review well-structured and organized? It is very structured and organized but its length and	

Section/ Page	Comment	Response
	bredth make it difficult to read and draw conclusions from. It really lacks a Conclusions section	
Overall/ general	• SRI question: Are the main points clearly presented? There needs to be a summary	
Overall/ general	• SRI question: Is it relevant to clinical medicine? The topic is relevant, it is hard to take anything useful away from all this information	
Dr. Michael Sailer (public comment)		
General	I highly suggest you start covering this intervention, as there is a large amount of level one evidence that it is effective for partial tendon tears in elbow, Achilles, and patellar tendon.	Thank you for your comment.

Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for hip resurfacing. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to robin@specri.com

If you have questions or concerns please contact Robin Hashimoto, PhD at the email above.

Reviewer Identification Information

Reviewer Name	**Alfred Gellhorn MD**
Address	**Street 525 E 68th St** **City New York** **State NY** **Zip Code 10065**
Phone	**212-746-1500**
Fax	**NA**
E-mail	**Alfg9**

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?
- Topic of assessment is important to address?
- Public policy and clinical relevance are well defined?

Page 61	Line

There appears to be no information included in the section: Washington State Utilization and Cost data.

Page 44 Line

Mention is made of the lack of standardization of PRP. This is an important point that may need additional explanation – given the multitude of kits for producing PRP on the market, and the various products generated therefrom.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page 62 Line

In general, the etiology of tendinopathy is not well understood. I think it is probably OK to call these a result of overuse, but there are a number of different theoretical bases for why tendinopathy develops. It may be worthwhile to point out that the lack of understanding about the physiologic basis of tendinopathy has led to the clinical situation where rational treatment options are limited.

Page 65 Line

It would be helpful to point out at some point in this section that conservative treatment options for degenerative tendinopathy and OA are in general quite limited and have inconclusive data for effectiveness. This is the background that provides frustration for both clinicians and patients – when patients present with one of these conditions, generally the clinician will offer NSAIDs, Tylenol, PT, steroid injection, and if these fail then proceed to surgical interventions. In the case of knee OA, the cost of a total knee replacement is very large, and if data on usage are extrapolated over the next 20 years, these costs will completely overwhelm our medical system. The search for biologic options represents a failure of mainstream conservative treatments.

Page 66 Line

ABI is just blood. In the mechanism of action section, it's suggested that ABI increases the concentration of platelets – not so. Additionally, the following statement is probably not correct either "platelets are the crux of PRP and ABI treatment" . ABI, since it's whole blood, doesn't try to concentrate or distill any factors from blood – more like simply creating a new injury in a chronically nonhealing location.

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?
- Key questions clearly defined and adequate for achieving aims?

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?

- Criteria for the inclusion and exclusion of studies is appropriate?
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
- Data abstraction and analysis/review are adequate?

Page	Line

Methods, inclusion and exclusion criteria, LoE ratings, and analysis plans are clearly outlined and appropriate

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate?
- Key questions are answered?
- Figures, tables and appendices clear and easy to read?
- Implications of the major findings clearly stated?
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

Page all Line

In general the forest plots are extremely helpful for visualizing the results. After reviewing all of the results, I was impressed by the consistency of the findings that PRP outcomes are favorable especially in the intermediate and long term time periods, regardless of the condition studied.

Page 102 Line

ABI vs PRP. Both of these approaches to treatments are biologically based, and share a theoretical framework. It's interesting to compare the differences in outcome between these approaches, but perhaps less interesting that comparing PRP against currently covered approaches that have different proposed mechanisms of action (eg steroid, Hyaluronic acid, exercise). The report also makes some comparisons between ABI and other conservative treatments (steroid, anesthetic) at various points (plantar fasciitis, elbow, Achilles eg), and so it's not completely clear whether we should be considering just PRP as the focus of the report, or ABI as a focus as well.

Page 195 Line

Cost effectiveness. The cost of PRP as well as the cost of other currently approved treamtents for tendinopathy and OA should have a larger role in the discussion. While the cost of steroid is low, the cost of other comparator treatments (HA, physical therapy, ESWT) are quite high. PRP cost varies by region and by kit, and is more or less up to the performing clinic to determine since there is no insurance coverage currently for the procedure. I am aware of PRP injections being offered at costs of $600-1500; these costs, while not insignificant, are probably less than comparator treatments that the report finds either equivalent to, or inferior to, PRP. What are the typical costs to insurance of PT 2 times a week x 6 weeks (a reasonable guess for treatment of tendinopathy or OA)? Costs for 3 HA injections twice a year? I suspect both of these would be much more expensive than an injection of PRP at average market rate.

It should also be noted quite strongly that throughout the results section PRP generally is superior to treatments that are currently covered, in the intermediate and long term results from the procedure. When PRP is not clearly superior, it is at least equivalent to treatments being performed. There are no data that indicate inferiority of PRP against current active treatments. While the quality of the evidence is frequently low and sometimes moderate, I get the very strong impression from the consistency of the results across various tendinopathies and OA that in the intermediate and long term, PRP is a superior treatment options when compared to pretty much all the comparitors.

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page	Line

I don't actually see any conclusions being drawn from the synthesized data. The report goes from the results section to the strength of evidence summaries – but I wouldn't necessarily call these conclusions. I would personally conclude the following from the included strength of evidence summaries:

PRP is superior to active control in the intermediate and long term in the treatment of elbow epicondylitis; in the long term in patellar tendinopathy; and in the short and intermediate term in rotator cuff tendinopathy

PRP is superior to HA in the treatment of knee OA in terms of function and pain in the intermediate and long term; and greatly superior to a saline placebo in short and medium term pain and function.

PRP is safe with a very favorable side effect profile.

The magnitude of the clinical improvements in the above conditions is clinically meaningful and important, especially in the setting of limited effective conservative treatments for tendinopathy and osteoarthritis.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?
- Are the main points clearly presented?
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?

Page	Line

Presentation of the report – while overwhelming in its size and breadth – is very well structured and organized. The results are clear and the language is clear. This is an important document for public policy.

QUALITY OF REPORT

Quality Of the Report (Click in the gray box to make your selection)
Superior x
Good
Fair
Poor

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

The form itself is not very user friendly. Tab doesn't jump easily between fields.

SPECTRUM RESEARCH

Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form

Reviewer Identification Information

Reviewer Name	**Kimberly G. Harmon**
Address	**4110 NE 142nd Street Seattle, WA 98125**
Phone	**206-769-7209**
Fax	**206-598-3140**
E-mail	**kharmon@uw.edu**

EXECUTIVE SUMMARY Comments

Page 1, para 2:
"PRP formulations usually contain at least a 200% increase from baseline platelet count.40" – While this is one definition some of the formulations that are included in the studies do not have that big of an increase. Arthrex ACS typically only has 1.2x baseline platelets. A better definition to encompass all PRP preparations on the market is that there is an increase of platelets over baseline.

Page 1, para 2:
"Although the method of preparation can greatly vary, PRP preparation involves at least one high-speed centrifugation to isolate a platelet-rich buffy coat layer." Many of the current systems do not isolate the buffy coat. All of the leukocyte-poor preparations are not buffy coat systems and isolate the RBCs from plasma with platelets still suspended. These spins are usually slower and not at long as buffy-coat systems. Because of this methodology, LP-PRP is usually 1.2 – 3X baseline level of platelets while buffy coat systems increase the platelet count to 5 – 9X baseline but also typically include WBCs.

Page 1, para 2
"It is common to add local anesthetic to PRP and ABI to reduce pain at the injection site." It is very uncommon to add local anesthetic to PRP or ABI. This was an older technique and, at least in the US, almost nobody does this. In fact, most people, if using anesthetic at all, only anesthetize the superficial tissues and not actual tendon. This is because of some research by Mazzococa that indicated the anesthetic may inhibit platelet function.

The exact same 3 paragraphs is repeated on page 44 under "Appraisal" and should be modified there as well.

APPRAISAL Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate?

The exact same 3 paragraphs is repeated on page 44 under "Appraisal" and should be modified per suggestions above.

- Topic of assessment is important to address?

The use of PRP and ABI in musculoskeletal conditions is common and it is important that it be addressed.

- Public policy and clinical relevance are well defined?

Yes.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient?

Page 62, "Epidemiology" 2.1.1
May be useful to include commonly cited fact that 30% - 50% of sports injuries are related to tendon (Kannus, 1997)

Page 62, "Tendinopathies" 2.1.2
It would be helpful to include more background about tendinopathies as this is where the vast majority of the studies included in the paper are. Some references/concepts to think about include the concept of tendon injury along a continuum, (Cook J, BJSM, 2009) , the fact that tendonopathy is not always activity related (Rolf 1997), and the concept of tendon pain and its relation to pathology (Rio E, Sports Med, 2014). Also the pathogenesis of tendinopathy (Liu P, Scan J Med Sci Sport, 2011).

There is also significant evidence that those with diabetes are more prone to tendinopathy (Ranger TA, BJSM, 2015) and some evidence that those with lipidemia have higher rates of tendinosis. (Tilley BJ, BJSM, 2015) Tendinosis can also be caused by flouroquinolones.

It should also be mentioned that treatment of tendinopathy is largely dependent on the stage on which the tendinopathy is treated with tendons that are end-stage disrepair unlikely to respond to much while other stages may respond to anything. There is no good way to clinically stage a tendon and thus most tendon studies include a heterogenous population of tendon stages and end up with about a 60% success rate (eccentric exercises, corticosteroid injections, ABI, PRP, etc).

Achilles Tendinopathy – Page 63
"Achilles tendinopathy typically results from microtears stemming from overuse of the Achilles tendon,236 although approximately 2% of cases are caused by chronic diseases such as a rheumatoid arthritis or other inflammatory joint diseases." This is probably not true. Please see above comments and literature references to the pathogenesis of tendinopathy including reference that up to 30% of severe cases of Achilles tendinopathy requiring surgery are not related to activity. (Rolf, 1997)

Rotator Cuff Tendinopathy – Page 63

"Rotator cuff tendinopathy is caused by shoulder impingement, which leads to a diminished vascular supply resulting in inflammation and degeneration of the tendon.24,263 This can be related to impingement but this is only one of many causes. It is estimated that 30% of asymptomatic people over 60 have partial tears and tendinopathy of the rotator cuff. There are a multitude of factors that go into the development of tendinopathy – not just overuse.

Acute Local Muscle Injury – Page 63/64
"Diagnosed through sonography, muscle injuries are detected as areas of aberrant muscle structure with small hematomas; they may appear hyperechoic.33" Although these can be diagnosed with ultrasound, they are typically diagnosed clinically, and many people with clinically diagnosed strains will not have ultrasound findings, especially acutely.

Osteochondral Lesions of the Talus – Page 64
"Osteochondral lesions to the talus are structural injuries to the cartilage and bone on the bottom of the ankle joint.244" - bottom of the ankle joint is not a very descriptive or particularly accurate way to describe this. More accurate would be "injuries to the cartilage and bone on the superior aspect of the talus" or just "in the ankle joint"

2.1.4. Osteoarthritis – page 64
More about the pathogenesis of OA is important. It is a breakdown of the articular surface of the bone which causes release of IL-1 and other cytokines causing the synovium to increase production of apoptotic cytokines. It is not inflammatory in the traditional sense of the word i.e. typically no cell mediated inflammation, but many inflammatory cytokines and chemokines. Although the pathogenesis is incompletely understood, more on current understanding would be helpful to help people understand the rationale behind the use of PRP

2.2. Technology: Platelet Rich Plasma and Autologous Blood Injections – page 66
You should add that PRP and ABI are considered mimimally manipulated and therefore exempt. Current wording is a little confusing.

2.2.2. Injection Procedure
"The process of obtaining PRP begins by drawing 20 to 60 mL of blood from the patient." Many commercially used kits require only 9 – 10 mL of blood. Your lower limit should be 9.

"but PRP preparation involves at least one high-speed centrifugation to separate the blood into an erythrocyte layer at the bottom, a buffy coat layer in the middle, and an acellular plasma layer at the top" – Not all PRP systems use the buffy coat, i.e. Cascade, Arthrex, Regenex, etc. In general LR-PRP systems use the buffy coat while LP-PRP systems do not.

"Dry needling is often done in conjunction with injections for tendinopathies and plantar fasciitis." – dry needling (although this is a little confusing because this is most often used to mean a physical therapy technique performed with acupuncture needles) or tenotomy (more accurate in the setting of PRP or ABI) is typically either performed by a practitioner or not – it is usually not tendon dependent. Many people to PRP or ABI without dry needling/tenotomy and many people include it.

"If treatment is in the knee, PRP or ABI will generally be injected intra-articularly" ABI is not generally used intra-articularly as this can cause damage. Probably instead of "knee" you should rephrase this to "If treatment is for osteoarthritis, PRP will generally . . . . " Treatment of patellar tendons, MCL, etc. are extra-articular and still about the knee.

"After injection, it is typically recommended that patients refrain from weight-bearing activities involving the injected joint for several days.´ Totally variable – this may be true with OA but often is not. I would say "After injection it is typically recommended that patients decrease activity for several days to several weeks"

2.3.1. Dry needling

"Dry needling describes the process of repeatedly passing a needle through the tendon to disrupt collagen fibers and induce bleeding without injecting any substance.71,110" I would clarify that this includes a heterogenous group of treatments ranging from treatments done with small acupuncture needles by physical therapist without anesthesia to treatments performed with large bore hypodermic needles performed by physicians with local anesthetic.

"Needling may be ultrasound-guided and a substance such as corticosteroid or PRP may be injected after disruption of the tendon.20,110 Peppering can be done with an injectate, such as autologous blood. The needle is inserted into the tendon and a portion of the fluid is injected, then withdrawn without emerging from the skin, redirected and reinserted into the tendon for additional injection.71,132" This is all very confusing for the lay person as in the previous sentence you mention needling and peppering with suggestion that what may be injected is different. Needling, tenotomy, dry needling, peppering are all terms that mean putting some sort of needle into the tendon. They are used somewhat interchangeably but sometimes will denote a specific technique i.e. dry needling is typically a physical therapy technique done with acupuncture needles, tenotomy is typically done with hypodermic needles by a physician, peppering and needling can also be used to denote this. You can inject something – corticosteroid, blood, or PRP after any of the techinques although typically that is only done by physicians who tend to use hypodermic needles.

2.3.2. Injections: Corticosteroids

"For the treatment of knee osteoarthritis, the American College of Rheumatology generally recommends the use of intra-articular corticosteroids.103" True but there is little evidence to support their use long term – same for tendons.

2.3.4. Injections: Hyaluronic Acid (HA)

More should be included on this modality as it is the major comparator in most OA studies. As you know, recently the AAOS recommended against the use of HA in OA based on doubtful evidence of clinical benefit, while other societies disagree with this analysis (American College of Rheumatology, American Medical Society for Sports Medicine). It is considered a standard treatment for OA in European and Asian countries.

2.3.6. Exercise
2.3.7. Extracorporeal Shock Wave Therapy (ESWT)
2.3.8. Low Level Laser Therapy

You have made statements regarding the effectiveness of these treatments and reference appropriately, however, there is much debate on whether many of these things – eccentric exercises, ESWT which is heterogeneous in how it is applied and used, and laser therapy work. I'm concerned that when there are statements about how these things work that are not held up to the same rigorous standards that you later hold up PRP and ABI that this may lead to erroneous interpretation of the evidence.

2.3.10. Surgery

"Surgery is usually the last option for tendinopathy treatment, as failure rates for debridement and/or decompression are has high as 20% to 30%.9" Failure rates in some studies are as high as 50% for tendon surgery – can't remember reference – recently did lit search on this

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue?

- The objectives and aims are clearly stated.
- Key questions clearly defined and adequate for achieving aims?

Yes.

METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate?

Yes

- Criteria for the inclusion and exclusion of studies is appropriate?

Yes

- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?

Yes

- Data abstraction and analysis/review are adequate?

Yes, although some of the subtleties in different studies are lost. I don't think you can include dry needling and corticosteroid injection in the same group. These are completely different treatments. I would compare separately to dry needling, corticosteroid injection or saline injection.

RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate

Yes, but there is no real synthesis for results. There are 80 pages of results but it is really hard to make anything of all these results without any clinical context. Hard, especially for someone without a great deal of clinical knowledge to understand the results presented in this format.

- Key questions are answered?

  Not really. The key questions are listed below. There are 80 pages of results with no conclusions to answer the questions below. I think you need to restate the questions, give concise summary answers in a "Conclusions" section.

Key questions:

1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?

Should there be a statement like "the evidence is limited by the heterogeneity of the study population, methods and comparators, in general it seems that there is a low degree of evidence that ABI/PRP is effective in intermediate and long-term pain and function in elbow epicondylitis compared to . . . . " or a more concise, readable summary table is needed.

2. What is the evidence regarding short- and long-term harms and complications of autologous PRP or whole blood injections compared with alternative treatment options or no treatment/placebo?

This requires a summary statement.

3. Is there evidence of differential efficacy, effectiveness, or safety of autologous PRP or whole blood injections compared with alternative treatment options no treatment/placebo? Include consideration of age, sex, race, ethnicity, socioeconomic status, payer, and worker's compensation?

4. What is the evidence of cost-effectiveness of autologous PRP or whole blood injections compared with alternative treatment options?

- Figures, tables and appendices clear and easy to read?

Yes – but need a summary figure that is concise and easy to read

- Implications of the major findings clearly stated?

Basically – no evidence see comments above.

- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature?

CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

There are no conclusions – a "conclusions" section is not outlined in the table and I could not find any conclusions other than individual results of different comparators. See discussion above in results section.

OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?

It is very structured and organized but its length and bredth make it difficult to read and draw conclusions from. It really lacks a Conclusions section

- Are the main points clearly presented?

There needs to be a summary

- Is it relevant to clinical medicine?

The topic is relevant, it is hard to take anything useful away from all this information

- Is it important for public policy or public health?

QUALITY OF REPORT

Quality Of the Report (Click in the gray box to make your selection)
Superior
Good
Fair

Poor

From: Dr. Michael J. Sailer [mailto:M.Sailer@proliancesurgeons.com]
Sent: Tuesday, March 01, 2016 5:36 PM
To: HCA ST Health Tech Assessment Prog
Subject: prp

I highly suggest you start covering this intervention, as there is a large amount of level one evidence that it is effective for partial tendon tears in elbow, Achilles, and patellar tendon.

Michael Sailer