



**Health Evidence Review  
Commission's  
Evidence-based Guideline  
Subcommittee**

**February 4, 2016  
2:00 PM**

**Clackamas Community College  
Wilsonville Training Center, Room 111-112  
29373 SW Town Center Loop E, Wilsonville, Oregon,  
97070**

# Section 1.0

## Call to Order

## AGENDA

### EVIDENCE-BASED GUIDELINES SUBCOMMITTEE (EbGS)

February 4, 2016

2:00pm - 5:00pm

Clackamas Community College  
Wilsonville Training Center, Rooms 111-112  
29353 SW Town Center Loop E  
Wilsonville, Oregon 97070

*Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed. Please sign-in to testify.*

#	Time	Item	Presenter
1	2:00 PM	Call to Order	Wiley Chan
2	2:05 PM	Review of November, 2015 minutes	Wiley Chan
3	2:10 PM	Staff update	Darren Coffman
4	2:15 PM	Review public comments a. Skin Substitutes for Chronic Skin Ulcers	Adam Obley Cat Livingston
5	3:00 PM	Review scope statements on potential new topics. a. 3D Mammography/Digital Breast Tomosynthesis for Screening Mammography b. Fecal Microbiota Transplants for C. Dificile c. Genetic tests for Antidepressant Therapy. d. Interventions to Reduce the Harms of Tobacco During Pregnancy e. Intestinal motility tests f. Long-Acting Reversible Contraceptives g. Percutaneous Interventions for Low Back Pain h. Treatments for Recurrent Acute Otitis Media (scoring only)	Adam Obley Cat Livingston
6	4:20 PM	Review scoring on above topics	Cat Livingston
7	4:45 PM	Confirmation of the next meeting, April 7, 2016	Wiley Chan
8	4:50 PM	Next Topics	Cat Livingston
9	5:00 PM	Adjournment	Wiley Chan

*Note: All agenda items are subject to change and times listed are approximate*

## MINUTES

### Evidence-based Guidelines Subcommittee

Clackamas Community College  
Wilsonville Training Center, Rooms 111-112  
29353 SW Town Center Loop E  
Wilsonville, Oregon 97070  
November 5, 2015  
2:00-5:00pm

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**Members Present:** Wiley Chan, MD, Chair; Eric Stecker, MD, MPH (arrived at 2:05), Vice-Chair; Vern Saboe, DC; Beth Westbrook, PsyD; George Waldmann, MD; Alison Little, MD, MPH.

**Members Absent:** Bob Joondeph, JD

**Staff Present:** Darren Coffman; Catherine Livingston, MD, MPH; Jason Gingerich.

**Also Attending:** Adam Obley, MD, Craig Mosbaek (Center for Evidence-Based Policy), CJ Dantine (OSIRIS), Dirk Sutherland (Alliqua Biomedical), Carol Howe and Lisa Chickadonz (American College of Nurse-Midwives), Jessie Little (OHA Actuarial Services), Erica Pettigrew (OHSU).

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#### 1. CALL TO ORDER

Wiley Chan called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:00 pm.

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#### 2. MINUTES REVIEW

Chan asked that the September minutes be corrected to show approval of the scope document on Neuroimaging for Headache.

**Minutes approved as amended 5-0 (Absent: Stecker).**

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#### 3. STAFF REPORT

Coffman welcomed Alison Little to the subcommittee, and announced that Vern Saboe will be rotating off of EbGS and onto VbBS when his HERC term ends at the end of the year. A new complimentary and alternative medicine representative is being sought for HERC, and when that person is appointed, they will join EbGS as well.

Coffman also suggested moving the November EbGS meeting to the first week of December in 2016. Waldmann said that date might be a problem for him. No decision was made.

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Coffman also reported that HERC decided to open public meetings in listen-only mode. Members of the public will be allowed to call in, but only invited speakers will receive a code to allow them to be heard.

Livingston gave an update on the Coverage Guidance on Planned Out-of-Hospital Birth. It was discussed at the October VbBS and HERC meetings but discussion will be continued in November, when it will likely be approved. Livingston said some more minor changes were being suggested, including requiring documenting the absence of certain risk factors, which would end up meaning HIV, syphilis and hepatitis B would require screening in addition to other risk factors. There are many implementation considerations for this coverage guidance; she asked for feedback on how the subcommittee felt about the level of detail they got to in the coverage guidance.

Waldmann said that lack of malpractice insurance is one of the considerations for CCOs; for that reason he confirmed that coverage of the birth itself for providers lacking liability insurance would be provided by fee-for-service Medicaid and the mother and child would return to CCO coverage after the labor and delivery. He expressed concern that OHA fee-for-service staff might not do as much precertification work as the CCOs, but Livingston said there is a nurse responsible for reviewing these cases.

Westbrook responded to Livingston's question, saying that it was a detailed discussion for out-of-hospital birth, but she was willing to go into details if needed. Chan said that the Value-based Benefits Subcommittee is more accustomed to dealing with such implementation details, but the EbGS seems to be getting into that territory more and more. Westbrook said she is comfortable doing that to the extent that the group is reviewing the evidence rather than speculating. Livingston noted that the skin substitutes coverage guidance will get into some policy speculation issues.

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#### **4. Review of public comment— Nitrous Oxide Use for Labor Pain Management**

Robyn Liu reviewed the single public comment, which focused on safety issues. The response is that the guidance assumes that the gas will be used by qualified personnel and used in a safe way. No changes were made to the draft coverage guidance.

Livingston reviewed some clarifying edits made by staff during the public comment period, shown in track changes in the meeting packet. There was no discussion of these edits.

Stecker asked about the billing codes. There is an anesthesia code for nitrous oxide but it can only be used by anesthesiologists and nurse anesthetists. In a hospital setting, nitrous oxide would be billed as part of a bundled payment. In the out-of-hospital settings, implementers will need to find a way to reimburse this service.

Livingston invited public comment. Carol House offered public comment. She recently retired as program director for the midwifery center at OHSU. She asked about the use of nitrous oxide during the delivery of the placenta. Liu clarified that the delivery of placenta is the third stage of labor, so would be included with the existing language.

**Motion to approve the draft coverage guidance for review by VbBS and HERC was approved 6-0.**

## DRAFT COVERAGE GUIDANCE

Nitrous oxide for labor pain is recommended for coverage (weak recommendation).

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### 5. Review need for updates on coverage guidances approved in 2013

For Induction of Labor, Liu reviewed the rescanning document. Livingston recommended not reviewing the topic as no change would be likely. After minimal discussion, the subcommittee voted 6-0 to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

For Recurrent Acute Otitis Media, Liu said this would likely be the most controversial. At the time that the coverage guidance was approved the American Academy of Pediatrics recommended use of prophylactic antibiotics. Liu said that there are new evidence reviews but they are poor quality and contradictory. The AAP no longer recommends use of prophylactic antibiotics, due in part to concerns about antibiotic resistance and limited benefit. Livingston said the staff recommendation is to review the topic again to address the AAP guideline as well as concerns about antibiotic resistance and adenoidectomies and tympanostomy tubes. After minimal discussion, the subcommittee voted 6-0 to recommend the development of a new coverage guidance on the topic.

For Neuroimaging for Headache, Livingston recommended not updating the coverage guidance until the next two-year cycle. After minimal discussion, the subcommittee voted 6-0 to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

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### 6. Review draft coverage guidance—Skin substitutes for chronic skin ulcers

Coffman introduced Dr. Foy White-Chu, who will serve as clinical expert for this topic. Dr. White-Chu is Associate Geriatric Fellowship Director at the Portland VA Medical Center. She is certified as a Physician Specialist in Wound Care by the Council for Medicine Education and Testing, and a Diplomate of the American Board of Internal Medicine, with Geriatric Medicine Subspecialty. For conflicts of interest, in addition to her employment, she provides clinical medical education training on wound care at regional conferences several times each year.

Liu reviewed the draft coverage guidance. Subcommittee members asked several questions about the regulatory context. Some of these products are FDA-approved and as such have approved indications for use. Others are said to qualify as human tissue products, which do not require such approval and thus are regulated differently for safe handling rather than clinical effectiveness. There is litigation over which products fall into which category. Livingston said initially that staff wanted to separate products by tissue type but discovered that this doesn't provide a useful distinction as the effectiveness of each product needs to be considered individually to determine efficacy.

When Liu reviewed the parameters for the literature search, Livingston mentioned that the original scope included only comparison to usual care, but the search also returned some head-to-head comparisons of different products. Stecker noted that there are problematic issues combining

comparisons to usual care and comparisons of multiple products. Livingston agreed and said that the subcommittee will discuss these where appropriate.

Liu also discussed that some industry stakeholders submitted studies that weren't found in staff's literature search because the articles were very recent or hadn't been indexed by MedLine. According to the Coverage Guidance methodology, these studies were not considered in the initial draft coverage guidance, but will be included if submitted as a part of public comments and reviewed along with other public comments. Staff has already notified stakeholders that they will need to resubmit the studies during the formal comment period. The search strategy included only systematic reviews, evidence-based guidelines meta-analyses and randomized controlled trials indexed in MedLine.

Before Liu reviewed the evidence around the eight products for which staff found evidence, Livingston explained that the staff recommendations were based on a requirement for at least low quality evidence of benefit to justify a coverage recommendation. No evidence that met inclusion criteria was found for the treatment of pressure ulcers, and evidence for many of the products was rated as very low quality, so coverage was not recommended for these. Staff also clarified the difference between the level of certainty about the outcome from what the outcome is. In some cases we have low certainty of benefit. This means that the evidence is weak and indicates that the product doesn't have a benefit for the selected outcome.

Livingston reviewed the cost issues. Some products are applied only once; others are applied multiple times with different maximum amounts for different products. She explained how the cost varies by setting of care and billing methodology for Medicare. Many of the costs are similar, but there are some outliers. Stecker questioned the usefulness of this analysis because of the higher variability. An insurer could instead approve spending for a particular dollar amount over a time period. Chan said that another approach would be to determine whether the benefit is cost effective. You would only compare costs if you had evidence of benefit for two products with different costs in the same application.

After Livingston and Liu reviewed the cost information, Stecker questioned the use of this level of detailed cost information. White-Chu explained that Apligraf is a perishable product sold in large sizes. Frequently much of the product is wasted because the wound is small, and she has had cases where the product was wasted because of shipping delays due to storms in the Midwest. Other products such as Epifix are sold in smaller sizes and have a long shelf life. Pricing evolves rapidly and depends on facility negotiations. Stecker expressed concern about going into this level of detail. For instance, with ablation for atrial fibrillation, payers don't specify the kinds of catheters a surgeon uses or what kinds of anesthesia or imaging he uses; using cost data in this way would go beyond the HERC coverage guidance on that topic. Westbrook said it may be worth these amounts to prevent an amputation; there needs to be room for clinicians to make decisions, including cost effectiveness decisions, for their patients.

Livingston then reviewed the Coverage Guidance box recommendation. Based on Liu's recommendation, Livingston endorsed changing the recommendation in the meeting materials for Oasis, changing it to a weak recommendation for coverage for diabetic foot ulcers based on the outcome of time to complete wound healing.

After discussion, the subcommittee decided to strike the paragraph on reference pricing and bundling, to leave such decisions to payers. In addition, the subcommittee revised the criteria for coverage of the products recommended for coverage. It moved requirements for offloading, multilayer compression dressings and tobacco cessation and made them part of the definition of prior appropriate wound care.

After discussion, the requirement for tobacco cessation was also changed to a requirement for participation in smoking cessation counseling. (The subcommittee didn't find sufficient evidence in this review to require smoking cessation, but did retain the requirement for provision of smoking cessation counseling.)

The subcommittee also added a requirement for an ABI (Ankle-Brachial Index) of 0.7 as evidence of adequate arterial blood flow.

The subcommittee added a definition of failure of conservative wound care as failing to achieve a 50 percent reduction in ulcer surface area. In place of the limit on additional use of products which had failed previously, the subcommittee added a clause requiring continued significant improvement at six week intervals for continued coverage. After extensive discussion, the subcommittee specifically decided not to add a maximum total duration for therapy or maximum number of applications for a particular product because of lack of evidence to support such a restriction. Coffman said that VbBS may consider putting an upper limit based on limited resources.

Livingston invited public comment.

CJ Dantine testified representing Osiris, manufacturer of Grafix. He addressed the exclusion criteria for the Lavery study discussed earlier, which was HbA1c >12, or ABI >1.3 or <0.7. He said Noridian recently changed its criteria from requiring smoking cessation to requiring patients to be advised to stop smoking. He described the Grafix products, and cited the NICE guidance which finds benefits from Grafix based on a randomized trial which was stopped early for overwhelming efficacy. He said 34 million Medicaid lives have access to Grafix right now. In addition Noridian recently removed Grafix from the noncovered list.

Livingston said that staff would review the recommendation on Grafix based on this study during the public comment period. Liu said that this study had been included but the quality had been downgraded to very low based on lack of description of randomization and concealment as well as potential funder bias. No changes were made to the coverage guidance based on this testimony.

The subcommittee also discussed the strength of recommendation for Apligraf. After discussion the subcommittee decided to leave the recommendation as weak.

**Motion to post the draft coverage guidance for public comment as amended was approved 6-0.**

*Staff note: After the meeting it was discovered that this part of Liu's presentation contained an error with respect to the OASIS Wound Matrix, so this change was removed from the version posted for comment. EbGS will discuss this matter along with the public comments.*

### DRAFT HERC Coverage Guidance

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are recommended for coverage (*weak recommendation*) when all of the following criteria are met:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable

3. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12.
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, , with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. Patients is able to adhere to the treatment plan

The following products are recommended/not recommended for coverage as shown below. All recommendations are weak recommendations except as specified.

Product	Diabetic foot ulcers	Venous leg ulcers
Dermagraft	Recommended	Not recommended
Apligraf	Recommended	Recommended
OASIS Wound Matrix	Not Recommended	Recommended
Epifix	Not recommended	Not recommended
Grafix	Not recommended	Not recommended
Graftjacket	Not recommended	Not recommended
Talymed	Not recommended	Not recommended
Theraskin	Not recommended	Not recommended
Other skin substitutes	Not recommended	Not recommended

The use of skin substitutes is not recommended for coverage of chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g. pressure ulcers) (*weak recommendation*).

## 7. ADJOURNMENT

The meeting was adjourned at 4:32 pm. The next meeting is scheduled for February 4, 2016 from 2:00-5:00pm in Room 111-112 of the Wilsonville Training Center.

# Section 2.0

## Coverage Guidances

# HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

## Table of Contents

Commenters.....	1
Public Comments .....	2
References Provided by Commenters .....	8

## Commenters

Identification	Stakeholder
A	Soluble Systems <i>[Submitted December 7, 2015]</i>
B	Smith & Nephew Advance Wound Management <i>[Submitted December 15, 2015]</i>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

### Public Comments

ID/#	Comment	Disposition
A1	<p>“We would like to request that Oregon Medicaid reconsider the current non-coverage recommendation of Theraskin based on the following conclusions obtained from previously submitted clinical data. Upon review of the included references, Theraskin is as effective and at least equivalent to products currently recommended for coverage by Oregon Medicaid (Apligraf and Dermagraft).”</p>	<p>Thank you for your comment. We will address each of these studies individually below.</p>
A2	<p>“The 2011 Landman’s study concluded that Theraskin healed (closed) 60% of previously non-progressing diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) at 12 weeks and 74% at 20 weeks.”</p>	<p>Because this is a non-comparative retrospective case series, it does not meet individual inclusion criteria for the evidence review.</p>
A3	<p>“DiDomenico’s 2011 study concluded that TheraSkin had a greater rate of wound healing than Apligraf, both at 12 weeks (66.7% vs. 41.3%) and 20 weeks (66.7% vs. 47.1%).”</p>	<p>This study is included in the systematic review by Snyder, Sullivan, &amp; Schoelles (2014), and has thus already been included in the evidence review for the draft coverage guidance. DiDomenico and colleagues did not report a test of statistical significance of the difference observed in the trial; the authors of the AHRQ report found that the difference was not statistically significant (p=0.21).</p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A4	<p>“Sanders 2014 clinical study showed wounds treated with TheraSkin are <u>twice</u> as likely to close by week 12, with half the number of grafts, versus wounds treated with Dermagraft.”</p>	<p>This manuscript is not indexed in Medline and therefore was not included in the evidence review. Furthermore, this small (n=23) RCT is of poor quality because of uncertainty about allocation concealment; baseline differences in study population (particularly with respect to number of diabetes medications, peripheral arterial disease, tobacco use and wound duration before treatment); differences in the number of office visits in each treatment group and use of offloading techniques; and inadequate blinding of participants, personnel, and outcomes assessors. Additionally, two authors are paid consultants of Soluble Systems and the research was funded by Soluble Systems.</p>
A5	<p>“Snyder, Sullivan and Schoelles 2012 (AHRQ Review included on page 26 of Oregon’s Draft Policy) evaluated the effectiveness of Apligraf and TheraSkin for DFUs with average wound sizes. The study also concluded that there were no significant differences reported in complete wound closure between the two products Apligraf 41% vs. Theraskin 67%, p=0.21.”</p>	<p>The AHRQ systematic review concluded that there is insufficient evidence to draw conclusions about the comparative effectiveness of Theraskin and Apligraf. The single trial that informed this comparison (DiDomenico, 2011) was a small (n=28) and imprecise trial deemed to be at moderate risk of bias by the authors of the AHRQ review.</p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A6	<p>“We respectfully recommend Oregon Medicaid to take into consideration that Theraskin is broadly and long accepted by the medical community and insurance carriers as medically and reasonably necessary therapy for the treatment of a broad range of chronic wound indications.</p> <ul style="list-style-type: none"> <li>○ All A/B <u>Medicare Administrative Contractors (MACs)</u> across the U.S., including Oregon, cover Theraskin.</li> <li>○ 41 <u>Medicaid</u> plans throughout the country, including many states surrounding Oregon, also provide Theraskin coverage.</li> <li>○ Many large <u>Private Health Plans</u> cover Theraskin including Regence, Kaiser, Cigna, Blue Cross Independence, HCSC (BCBS IL/NM/OK/TX), Amerihealth, BCBS Highmark, United Health Care, Tricare, UPMC Health Plan, etc.”</li> </ul>	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that Theraskin is commonly, but not uniformly, covered.</p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
A7	<p>“Oregon Medicaid proposes a recommendation of non-coverage for Theraskin due to ‘product cost being moderate compared to alternative treatment options.’</p> <p>Listed within the Oregon Medicaid draft policy under ‘Frequency of application and cost of skin substitute’ Apligraf and Dermagraft product costs were based upon clinical studies while Theraskin’s product cost was based upon Medicare LCD limits. Thus, causing Theraskin associated cost-savings to appear modest when compared to alternative treatments.</p> <p>We respectfully recommend that Oregon Medicaid reevaluate Theraskin’s product cost in a similar manner as Apligraf and Dermagraft or adults <u>all</u> product cost using Medicare’s’ LCFD maximum limits.”</p>	<p>The right-hand column of the frequency of application document presented to EbGS was based on the maximum number of applications from the study, while lower limits were used for other products. The rationale column does note that most patients in the study only required a single application.</p> <p>At its November 3, 2015 meeting, the subcommittee recognized that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level. Therefore we have removed a specific number of applications for each product from the right column of the applications table and added information on application frequency used in the studies for those products recommended for coverage.</p> <p>However, the subcommittee still finds insufficient evidence of effectiveness to recommend this product for coverage.</p> <p><i>For EbGS discussion</i></p>
B1	<p>“In the draft guidance, the Commission recommends (with a weak recommendation) coverage of OASIS Wound Matrix for venous leg ulcers (‘VLU’). We support the recommendation for coverage of OASIS for VLU, and we thank the Commission for its position.”</p>	<p>Thank you for your comment.</p>
B2	<p>“By contrast, the Commission recommends against coverage of OASIS Wound Matrix for the treatment of diabetic foot ulcers (‘DFU’) concluding that there is ‘inadequate evidence of benefit, other alternatives available, and its costliness.’ We respectfully disagree with this recommendation for the reasons summarized below.</p>	<p>The study by Cazzell and colleagues was not indexed in Medline at the time of the search; it has subsequently been indexed. The previous RCTs of Oasis for DFU were included in the AHRQ review. Landsman, et al (2008) found no statistically significant difference between OASIS and</p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
	<p>There is new evidence, published after the 2012 Agency for Healthcare Research &amp; Quality ('AHRQ') systematic review from supporting the use of OASIS in the treatment of diabetic foot ulcers. This evidence was not considered by the Commission.</p> <p>The findings from a prospective, randomized controlled trial of OASIS Ultra Trilayer Matrix versus standard care were published in 2015 in <i>Advances in Wound Care</i>. In this 16 week trial, 82 qualified patients were randomly assigned to 12 weeks' treatment with OASIS or standard care. The trial demonstrated that a greater proportion of the DFUs were closed by the end of the treatment period (week 12) for the OASIS group than for the standard care group (54% vs. 32%; <math>p = 0.021</math>). More ulcers were closed at each weekly study visit in the OASIS group than the standard care group beginning at week 3 (first visit showing ulcers closed). The overall treatment effect on proportion of ulcers closed over the 12 weeks and the interaction of treatment by week were found to be statistically significant (<math>p = 0.047</math>) in favor of the OASIS group.</p> <p>In the draft coverage guidance, the Commission defined five outcomes considered in its evaluation:</p> <ul style="list-style-type: none"> <li>▪ Critical Outcomes <ul style="list-style-type: none"> <li>– Deep soft tissue or bone infection</li> <li>– Complete wound healing</li> </ul> </li> <li>▪ Important Outcomes <ul style="list-style-type: none"> <li>– Quality of life</li> <li>– Time to complete wound healing</li> <li>– Adverse effects</li> </ul> </li> </ul> <p>The randomized, controlled study above included three of these outcomes and supports the use of OASIS compared to the standard care with statistically significant results.”</p>	<p>Dermagraft for DFU wound healing at 12 weeks. Niezgoda, et al (2005) compared OASIS to Regranex Gel and found a difference in healing at 12 weeks that approached statistical significance (49% vs 28% respectively, <math>p=0.06</math>).</p> <p>Cazzell is an open-label RCT of 82 patients comparing OASIS to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator (standard care included sliver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group (54%) compared with the standard care group (32%) (<math>p=0.021</math>). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and inadequate blinding, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.</p> <p><i>For EbGS discussion.</i></p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
B3	<p>“OASIS has the same level of general acceptance by the medical community as Apligraf.</p> <p>While not a consideration for coverage, the Commission does review the policy landscape and payer coverage policies. Under Medicare, with respect to local coverage determinations, the policy must be based on published authoritative evidence derived from definitive RCTs or other definitive studies, and general acceptance by the medical community (standard of practice), as supported by sound medical evidence. Use of OASIS in the treatment of DFU is well established in the payer community:</p> <ul style="list-style-type: none"> <li>▪ All of the MACs cover OASIS for VLU and DFU</li> <li>▪ OASIS has positive coverage based on medical necessity from 760 private payers”</li> </ul>	<p>Thank you for your comment. Our review of Local Coverage Determinations (LCDs) as well as the policies of selected Medicaid programs and private health plans found that OASIS is commonly, but not uniformly, covered.</p>
B4	<p>“OASIS is the least costly product per application compared with Apligraf and Dermagraft.</p> <p>The Commission’s recommendation against coverage for OASIS for DFUs is based, in part, on the Commission’s conclusion that the product is costly. In fact, as is shown below, OASIS has a lower cost per application compared with Apligraf and Dermagraft—two other products recommended for coverage for diabetic foot ulcers.” <i>See chart in submitted comments.</i></p>	<p>OASIS does have a lower unit cost than Apligraf and Dermagraft. However, as noted in the cost comparison chart, studies which showed effectiveness of OASIS used 8 to 10 applications of this product per patient versus smaller quantities used in the studies showing effectiveness for Dermagraft and Apligraf.</p> <p>The subcommittee does recognize that costs and number of applications will vary by patient and that the cost of these products cannot be easily estimated at the population level.</p> <p><i>For EbGS discussion</i></p>

## HERC Coverage Guidance – Skin Substitutes Disposition of Public Comments

ID/#	Comment	Disposition
B5	“The Commission stated in the draft guidance that OASIS ‘is not recommended for coverage for diabetic foot ulcers based on inadequate evidence of benefit, other alternatives available, and its costliness.’ We believe that this new evidence, together with the position taken by private and public payers as well as the relative low cost of OASIS compared to Apligraf and Dermagraft, support coverage for OASIS for the treatment of diabetic foot ulcers.”	Thank you for your comment.  <i>For EbGS discussion.</i>

### References Provided by Commenters

ID/#	References
A2	Landsman A. S., Cook J., Cook E., Landsman A. R., Garrett P., Yoon J., Kirkwood A., Desman E. (2011). A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. <i>Foot Ankle Spec.</i> 4(1):29-41. DOI: 0.1177/1938640010387417.
A3	DiDomenico, L., Landsman, A. R., Emch, K. J., Landsman, A. (2011). A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. <i>Wounds</i> , 23(7):184-9.
A4	Sanders, L., Landsman, A. S., Landsman, A., Keller, N., Cook, J., Cook, E., Hopson, M. (2014). A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. <i>Ostomy Wound Manage</i> , 60(9):26-38
B2	Cazzell, S. M., Lange, D. L., Dickerson, J. E. Jr., Slade, H. B. (2015). The Management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: A randomized controlled trial. <i>Adv Wound Care</i> , 4:1-8. DOI: 10.1089/wound.2015.0645.

# HEALTH EVIDENCE REVIEW COMMISSION (HERC)

## COVERAGE GUIDANCE: SKIN SUBSTITUTES FOR CHRONIC SKIN ULCERS

**DRAFT for EbGS meeting materials 2/4/2016**

### HERC Coverage Guidance

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are recommended for coverage (*weak recommendation*) when all of the following criteria are met:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12.
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, , with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. Patients is able to adhere to the treatment plan

The following products are recommended/not recommended for coverage as shown below. All recommendations are weak recommendations except as specified.

Product	Diabetic foot ulcers	Venous leg ulcers
Dermagraft	Recommended	Not recommended
Apligraf	Recommended	Recommended
OASIS Wound Matrix	<del>Not</del> Recommended	Recommended
Epifix	Not recommended	Not recommended
Grafix	Not recommended	Not recommended
Graftjacket	Not recommended	Not recommended
Talymed	Not recommended	Not recommended
Theraskin	Not recommended	Not recommended
Other skin substitutes	Not recommended	Not recommended

The use of skin substitutes is not recommended for coverage of chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g. pressure ulcers) (*weak recommendation*).

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description*.

## **RATIONALE FOR GUIDANCE DEVELOPMENT**

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows standard methodology to translate evidence reviews into a policy decision. Coverage guidances are based on a thorough review of the evidence by the Evidence-based Guideline Subcommittee or the Health Technology Assessment Subcommittee. The evidence review used in the coverage guidance development process may use existing systematic reviews of the evidence on a given topic and incorporate additional individual studies published more recently than the included systematic reviews. Included evidence sources are generally published within the last three to five years. A full description of the evidence review methodology is included in each coverage guidance as an appendix. The translation of the evidence review to a policy decision is based on a GRADE-informed framework, as described below.

## GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are several elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

Note: The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee. The GRADE framework elements are described in Appendix A. A GRADE Evidence Profile is provided in Appendix B.

### Apligraf® / Graftskin

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	DFU <sup>1</sup> : osteomyelitis 2.7% vs 10.4% (p = 0.4) ●●○○ (low certainty of no benefit, based on one good quality RCT)  DFU (Apligraf vs Theraskin): One amputation due to infection with Theraskin vs none for Apligraf (p-value not reported) ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)	Incremental cost for adding Apligraf to a patient's course of treatment for a small leg ulcer (<25 cm <sup>2</sup> ) under Medicare FFS (using average national prices for October, 2015) would range from \$771.20 for a single application in an ambulatory surgery center to \$4,553.81 for three applications in the physician's office setting. Prices are

<sup>1</sup> DFU: Diabetic Foot Ulcer; VLU: Venous Leg Ulcer

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
	<p><u>VLU</u>: osteomyelitis 8.1% vs 0% (no statistical analysis) ●○○○ (very low certainty of benefit, based on one good quality RCT)</p>	<p>somewhat higher for foot ulcers due to higher physician fees/bundled fees for application. Product is sold in 44 cm<sup>2</sup> sheets. Up to 3 applications appear to be the maximum necessary based on included studies.</p>
<b>Complete wound healing</b> (Critical outcome)	<p><u>DFU</u>: RR 1.5, 1.96 (p = 0.01, 0.03) ●●●○ (moderate certainty of benefit, based on two good quality RCTs)</p> <p>DFU (Apligraf vs Theraskin): 47.1% vs 66.7% (p-value not reported) ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: RR 2.38 (p &lt; 0.001) ●●○○ (low certainty of benefit, based on one good quality RCT)</p> <p><u>Unspecified non-healing ulcers</u>: 100% vs 75% (p &lt; 0.01) ●○○○ (very low certainty of benefit, based on one poor quality RCT)</p>	
<b>Quality of life</b> (Critical outcome)	No evidence identified.	
<b>Time to complete wound healing</b>	<p><u>DFU</u>: No evidence identified.</p> <p><u>VLU</u>: 61 vs 191 days (statistical analysis not provided) ●●○○ (low certainty of benefit, based on one good quality RCT)</p>	

Coverage question: Should Apligraf® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
(Important outcome)	<p><u>Unspecified non-healing ulcers</u>: 7 vs 51 weeks (statistical analysis not provided)</p> <p>●○○○ (very low certainty of benefit, based on one poor quality RCT)</p>	
<b>Adverse effects</b> (Important outcome)	<p><u>DFU</u>: Pooled data from 4 RCTs showed similar incidence of cellulitis, dermatitis, and peripheral edema with Apligraf® vs control (statistical analysis not reported)</p> <p>●●○○ (low certainty of no harm, based on four good quality RCT)</p> <p><u>VLU</u>: Infection rates of 8.2% vs 7.8% (statistical analysis not reported)</p> <p>●○○○ (very low certainty of no harm, based on one good quality RCT)</p>	
<p><b>Rationale:</b> Apligraf is recommended for coverage for venous leg ulcers and diabetic foot ulcers, based on improved complete wound healing, low variability in patient preference, and despite its cost. A strong recommendation was not made because only 2/5 of the predefined critical/important outcomes were addressed by the evidence and in favor of Apligraf for DFU. Coverage is recommended only when other conditions exist for wound healing (see Other Considerations section, below).</p>		
<p><b>Recommendation:</b> Apligraf is recommended for coverage for diabetic foot ulcers and venous leg ulcers (<i>weak recommendation</i>) when conditions necessary for wound healing are present. Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 44 cm<sup>2</sup> and has a short shelf life, which may lead to waste.</p>		

## DermaGraft®

Coverage question: Should DermaGraft® be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	<p><u>DFU</u>: Osteomyelitis incidence 8.6% in both intervention and control groups</p> <p>●○○○ <i>(very low certainty of no benefit, based on one fair quality RCT)</i></p>	<p>Incremental cost for adding DermaGraft® to a patient's course of treatment for a small leg ulcer (&lt;25 cm<sup>2</sup>) under Medicare FFS (using average national prices for October, 2015) would range from \$771.20 for a single application in an ambulatory surgery center to \$11,960.80 for eight applications in the hospital outpatient setting. Up to 4 applications total appears equivalent efficacy to 8 applications.</p> <p>Product is sold in 37.5 cm<sup>2</sup> sheets.</p>
<b>Complete wound healing</b> <i>(Critical outcome)</i>	<p><u>DFU</u>: OR 1.64 (95% CI, 1.10 to 2.43) in pooled data from 3 fair quality RCTs; one poor quality RCT with 38.5% versus 31.7% (p = 0.138)</p> <p>●●○○ <i>(low certainty of benefit, based on three fair quality concordant RCTs and one poor quality discordant RCT)</i></p> <p><u>DFU (DermaGraft vs OASIS)</u>: 84.6% vs 76.9%, p = 0.62</p> <p>●○○○ <i>(very low certainty of no comparative benefit, based on one fair quality RCT)</i></p> <p><u>VLU</u>: RR 1.83 (95% CI, 0.47 to 7.21) and RR 3.04 (95%, CI 0.95 to 9.68) ●○○○ <i>(very low certainty of no benefit, based on two fair quality RCTs)</i></p>	
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.	
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	<p><u>DFU</u>: 13 weeks vs 28 weeks (statistical analysis not reported)</p> <p>●●○○ <i>(low certainty of benefit, based on four poor to fair quality RCTs)</i></p>	

	<p>DFU (Dermagraft vs OASIS): 40.90 vs 35.67 days, p = 0.73  ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)</p> <p><u>VLU</u>: 35 weeks vs 74 weeks, (statistical analysis not reported)  ●○○○ (very low certainty of benefit, based on one fair quality RCT)</p>	
<p><b>Adverse effects</b> (Important outcome)</p>	<p><u>DFU</u>: 19% vs 32%, p = 0.007; second RCT no difference in rates of AE.  ●○○○ (very low certainty of benefit, based on two fair quality RCTs)</p> <p><u>VLU</u>: Similar number of AEs in all groups, statistical analysis not reported  ●○○○ (very low certainty of no harm, based on one fair quality RCT)</p>	
<p><b>Rationale:</b> Dermagraft is recommended for coverage for diabetic foot ulcers based on evidence of reduced time to wound healing and a higher likelihood of complete wound healing than usual care, with low variability in patient values and preferences. The recommendation is weak because of the low certainty of the evidence, and relatively high cost.  Dermagraft is not recommended for coverage for venous leg ulcers based on insufficient evidence of benefit for any critical or important outcome and lack of FDA approval for this indication.</p>		
<p><b>Recommendation:</b>  Dermagraft is not recommended for coverage for venous leg ulcers (<i>weak recommendation</i>)  Dermagraft is recommended for coverage for diabetic foot ulcers (<i>weak recommendation</i>) when conditions necessary for wound healing are present.  Payers may wish to consider bundled payment, reference pricing, or other effective alternatives for smaller ulcers, as this product is sold in units of 37.5 cm<sup>2</sup> and has a short shelf life, which may lead to waste.</p>		

## OASIS® Wound Matrix

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
Deep soft tissue or bone infection <i>(Critical outcome)</i>	No evidence identified.	Incremental cost for adding OASIS Wound Matrix to a patient's course of treatment for a small leg ulcer (<25 cm <sup>2</sup> ) under Medicare FFS (using average national prices for October, 2015) would be \$235.69 for a single application in an ambulatory surgery center. In a physician's office, the cost would be \$10.72 per cm <sup>2</sup> plus physician's fees of \$143.73. The manufacturer recommends re-application every three to seven days as needed.  Product is sold in units of varying sizes, the smallest of which is 10.5 cm <sup>2</sup> . <a href="#">One study of DFU showed an average of 10 sheets. One study of VLU reported an average of 8 sheets. Study showed equivalence of 8 sheets of Oasis to 3 sheets of Dermagraft.</a>
Complete wound healing <i>(Critical outcome)</i>	DFU: 49% vs 28% (p = 0.06) <a href="#">at 12 weeks</a> ; 54% vs 32% (p=0.021) <a href="#">at 12 weeks</a> ●○○○ <del>(very low certainty of benefit, based on one fair quality RCT)</del> ●○○○ <a href="#">(low certainty of benefit, based on two fair quality RCTs with inconsistency in comparator groups)</a>  DFU (OASIS vs Dermagraft): 76.9% vs 84.6%, p = 0.62 ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT)  VLU: 80% vs 65% at 8 weeks (p < 0.05); 83% vs 46% at 16 weeks (p < 0.001); 55% vs 34% at 12 weeks, (p = 0.02) ●●○○ (low certainty of benefit, based on three fair to good quality RCTs with inconsistency in comparator groups)	
Quality of life <i>(Critical outcome)</i>	No evidence identified.	

Coverage question: Should OASIS® Wound Matrix be recommended for coverage for treatment of chronic skin ulcers?		
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource allocation
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	<u>DFU</u> : 5.4 vs 8.3 weeks, statistical analysis not reported; 67 vs 73 days (p = 0.245) ●○○○ (low certainty of no benefit, based on two fair quality RCTs) <u>DFU (OASIS vs Dermagraft)</u> : 35.67 vs 40.90 days, p = 0.73 ●○○○ (very low certainty of no comparative benefit, based on one fair quality RCT) <u>VLU</u> : 63% vs 40% expected to heal at 12 weeks, p = 0.0226 ●○○○ (very low certainty of benefit, based on one good quality RCT)	<a href="#">One Medicare LCD limits to 12 weeks of therapy.</a>
<b>Adverse effects</b> <i>(Important outcome)</i>	<u>DFU</u> : Approximately equal number of AEs between groups, statistical analysis not reported ●○○○ (very low certainty of no benefit, based on one fair quality RCT) <u>VLU</u> : Approximately equal number of AEs between groups, statistical analysis not reported ●○○○ (very low certainty of no benefit, based on one good quality RCT)	
<b>Rationale:</b> OASIS Wound Matrix is recommended for coverage for venous leg ulcers based on low-certainty evidence that it improves complete wound healing and time to complete wound healing, with low variability in values and preferences. OASIS Wound matrix is <del>not</del> recommended for coverage for diabetic foot ulcers based on <a href="#">low certainty -inadequate-</a> evidence of benefit <a href="#">of improved wound healing, low variability in values and preferences.</a> <del>other alternatives available, and its costliness.</del>		
<b>Recommendation:</b> OASIS is <del>not</del> recommended for coverage for diabetic foot ulcers <a href="#">and venous leg ulcers (weak recommendation).</a> <del>OASIS is recommended for coverage for venous leg ulcers (weak recommendation).</del> when conditions necessary for wound healing are present.		

## EpiFix®

Coverage question: Should EpiFix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Complete wound healing</b> <i>(Critical outcome)</i>	DFU: 92% versus 8% (p < 0.0001) ●○○○ <i>(very low certainty of benefit, based on one RCT of fair quality)</i>
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	No evidence identified.
<b>Adverse effects</b> <i>(Important outcome)</i>	No evidence identified.
<b>Rationale:</b> EpiFix is not recommended for coverage due to insufficient evidence of effectiveness and the availability of effective alternatives <i>(weak recommendation)</i> .	
<b>Recommendation:</b> EpiFix is not recommended for coverage for chronic skin ulcers <i>(weak recommendation)</i> .	

## Grafix®

Coverage question: Should Grafix® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Deep soft tissue or bone infection (Critical outcome)	DFU: "Wound-related infection" (undefined) 18.0% vs 36.2%, p = 0.044 ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Complete wound healing (Critical outcome)	DFU: 62% vs 21%, p < 0.01 ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Quality of life (Critical outcome)	No evidence identified.
Time to complete wound healing (Important outcome)	DFU: 42 days vs 69.5 days (statistical analysis not reported) ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
Adverse effects (Important outcome)	DFU: 44% vs 66% (p = 0.031) ●○○○ (very low certainty of benefit, based on one RCT of poor quality)
<b>Rationale:</b> Grafix is not recommended for coverage for <del>any indication</del> chronic skin ulcers due to insufficient evidence of effectiveness and the availability of effective alternatives ( <i>weak recommendation</i> ).	
<b>Recommendation:</b> Grafix is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## Graftjacket®

Coverage question: Should Graftjacket® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> (Critical outcome)	One trial had a single pt with hallux amputation due to infection in the treatment group and zero in control. ●○○○ (very low certainty of harm, based on one RCT of poor quality)
<b>Complete wound healing</b> (Critical outcome)	<u>DFU, vs moist dressing</u> : 70% vs 46% (p = 0.03) <u>DFU, vs Curasol</u> : 86% vs 29% (p = 0.006) ●●○○ (very low certainty of benefit, based on two poor to fair quality RCTs)
<b>Quality of life</b> (Critical outcome)	No evidence identified.
<b>Time to complete wound healing</b> (Important outcome)	<u>DFU</u> : 11.92 vs 13.5 weeks and 5.7 vs 6.8 weeks, not significant ●○○○ (very low certainty of no benefit, based on two poor to fair quality RCTs)
<b>Adverse effects</b> (Important outcome)	<u>DFU</u> : Wound infection 21.4% vs 35.7%, statistical analysis not reported ●○○○ (very low certainty of no harm, based on one poor quality RCT)
<b>Rationale:</b> Graftjacket is not recommended for coverage because of the very low evidence of benefit for the critical outcome of complete wound healing, and a lack of efficacy for improving time to complete wound healing. Given only one application is required, fewer resources would be needed which would be an argument in favor, however, there is insufficient evidence to justify if even at the lower cost, this would provide significant benefit to patients.	
<b>Recommendation:</b> Graftjacket is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## Talymed®

Coverage question: Should Talymed® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Complete wound healing</b> <i>(Critical outcome)</i>	<u>VLU</u> : 86% vs 45% (p = 0.0005) ●○○○ <i>(very low certainty of benefit, based on one good quality RCT)</i>
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	No evidence identified.
<b>Adverse effects</b> <i>(Important outcome)</i>	<u>VLU</u> : No significant treatment-related AEs ●○○○ <i>(very low certainty of no benefit, based on one good quality RCT)</i>
<b>Rationale:</b> Talymed is not recommended for coverage because of very low certainty of benefit, a lack of strong patient preferences for this, alternatives available, and its high cost.	
<b>Recommendation:</b> Talymed is not recommended for coverage for chronic skin ulcers <i>(weak recommendation)</i> .	

## TheraSkin®

Coverage question: Should Theraskin® be recommended for coverage for treatment of chronic skin ulcers?	
Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
<b>Deep soft tissue or bone infection</b> <i>(Critical outcome)</i>	DFU (Theraskin vs Apligraf): One amputation for infection, compared to none with Apligraf ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
<b>Complete wound healing</b> <i>(Critical outcome)</i>	DFU (Theraskin vs Apligraf): 66.7% vs 41.3% (p = 0.21) ( <del>p-value not reported</del> ) ●○○○ (very low certainty of no comparative benefit, based on one RCT of fair quality)
<b>Quality of life</b> <i>(Critical outcome)</i>	No evidence identified.
<b>Time to complete wound healing</b> <i>(Important outcome)</i>	No evidence identified.
<b>Adverse effects</b> <i>(Important outcome)</i>	No evidence identified.
<b>Rationale:</b> Theraskin is not recommended for coverage because of insufficient evidence of benefit (limited evidence suggesting it is comparable to another effective product), a lack of strong patient preferences for this, alternatives available, and its moderate-cost.	
<b>Recommendation:</b> TheraSkin is not recommended for coverage for chronic skin ulcers ( <i>weak recommendation</i> ).	

## EVIDENCE OVERVIEW

### Clinical background

Diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and decubitus ulcers can be serious wounds, leading to severe health outcomes such as amputations and death. Diabetic foot ulcers are the result of atherosclerosis that impedes blood flow to the extremities and peripheral neuropathy that reduces the ability to sense injuries from extended pressure or other causes. Diabetic foot ulcers can lead to infections such as osteomyelitis and amputation. Appropriate treatment of these wounds can minimize the negative health outcomes and improve patient quality of life. Treatment for diabetic foot ulcers include cleaning, dressing, debridement, and pressure relief (Wound, Ostomy, and Continence Nurses Society, 2012). During the past 20 years, the prevalence of diabetes among adults in Oregon has more than doubled, to 9% in 2011. Among adults covered by the Oregon Health Plan, 17% have diabetes (Oregon Heart Disease and Stroke and Diabetes Prevention Programs, 2013). The annual incidence of foot ulcers among Medicare patients with diabetes is 6% (Margolis et al., 2011).

Venous leg ulcers are caused by chronic venous insufficiency. Treatment for venous leg ulcers include cleaning and dressing the wound, hemodynamic support to control the underlying disorder that caused the ulcer (e.g., medication or vascular bypass procedures), compression bandages, and compression stockings. The lifetime incidence of venous leg ulcers is about 1% (O'Meara, Al-Kurdi, & Ovington, 2008).

Decubitus ulcers or pressure ulcers (commonly called bed sores or pressure ulcers) occur when patients are unable to reposition themselves, most commonly in hospitals, long-term care facilities, and at home. Sustained pressure on a specific part of the body (often a bony prominence such as hip or sacrum) for long periods of time can cause a pressure ulcer. Treatment includes removing the pressure from the affected area, skin protection, debridement of necrotic tissues, cleaning, and dressing. Data from the National Nursing Home Survey indicate that 11% of nursing home residents had pressure ulcers (Park-Lee & Caffrey, 2009).

Skin substitutes have been used to treat ulcers that do not heal with the standard treatments. The most common use for skin substitutes is for the treatment of diabetic foot ulcers, venous leg ulcers, and decubitus ulcers. The etymologies of these ulcers make the wounds slower to heal, and the usual wound treatments are not always sufficient to ensure complete healing.

### Indications

Skin substitutes are indicated for the treatment of chronic wounds, usually defined as having not healed within 30 days, having not responded to initial treatment, or persisting despite appropriate care. Skin substitutes were originally designed to treat burns, but now the most common usage is treating diabetic foot ulcers, venous leg ulcers, and decubitus ulcers.

## Technology description

Skin substitutes promote healing and wound closure by mimicking or substituting for the skin structure. The skin substitute is designed to help the healing process by stimulating the host to regenerate lost tissue and replace the wound with functional skin. Skin substitutes can be categorized (Snyder, Sullivan, & Schoelles, 2012) based upon how they are derived or produced:

- Products derived from human donor tissue
- Products derived from living human or animal tissues and cells
- Acellular animal –derived products
- Biosynthetic products

Currently, there are over 73 skin substitute products approved by the FDA for use in humans. While skin substitute products can be broadly grouped according to their source materials, the products are all sufficiently unique as to make generalization of efficacy across categories impracticable.

Table 1 shows skin substitute products available in the United States, categorized by how the product is derived and thus regulated by the FDA. This list of skin substitutes was created from the evidence and policy sources, and may not be complete. Products in the same category may not be equivalent in terms of effectiveness (Snyder, Sullivan, & Schoelles, 2012).

Human-derived skin substitute products that are minimally processed are regulated by the FDA as human cells, tissues, and cellular and tissue-based products (HCT/Ps). With HCT/Ps, tissue is obtained from human donors then processed and used in the same role in the patient (e.g., skin for skin, tendon for tendon). These HCT/Ps are regulated as human tissue intended for transplantation as long as the processing and clinical use are consistent with “Minimal Manipulation” and “Homologous Use” as defined in 21 CFR 1271. Products regulated as HCT/Ps must be registered with the FDA but are not required to demonstrate safety or effectiveness.

Cellular-derived material for wound healing cultured from human-derived tissues are regulated using the Biologics License Application (under the Federal Public Health Service Act) or with premarket approval (PMA) or as a Humanitarian Use Device obtained through a humanitarian device exemption depending on their composition and primary mode of action. The application for products regulated under the PMA process must include scientifically valid clinical studies demonstrating that the product is effective and safe.

Acellular animal-derived products and synthetic products are regulated under Section 510(k) of the Food, Drug and Cosmetic Act. This requires a premarket submission to the FDA to demonstrate that the device is substantially equivalent, i.e., at least as safe and effective, to a legally marketed device that is not subject to PMA. Submitters can compare their device to a device that was legally marketed prior to May 28, 1976 or a device which has been previously found to be substantially equivalent through the 510(k) process (Snyder, Sullivan, & Schoelles, 2012).

**Table 1: Skin Substitutes**

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
AlloDerm Regenerative Tissue Matrix Allpatch HD™ Alloskin™ Cymetra® Micronized AlloDerm Dermacell® and Arthroflex® Flex HD® GammaGraft® Graftjacket® Regenerative Tissue Matrix Graftjacket® Express Scaffold Matrix HD™ Memoderm™ Puros® Dermis Repliform® TheraSkin®	Apligraf®/Graftskin Dermagraft® AlloMax™ Celaderm® OrCel™ TransCyte™	Acell UBM Hydrated Wound Dressing Acell UMB Lyophilized Wound Dressing Aongen™ Collagen Matrix Atlas Wound Matrix Avagen Wound Dressing Biobrane® Collagen Sponge (Innocoll) Collagen Wound Dressing (Oasis Research) Collaguard® CollaSorb™ CollaWound™ Collexa® Collieva® Coreleader Colla-Pad Dermadapt™ Wound Dressing DressSkin EndoForm Dermal Template™ Excellagen E-Z Derm™ FortaDerm™ Wound Dressing Helicoll Integra® Dermal Regeneration Template	Epicel™ Hyalomatrix® (Laserskin®) Hyalomatrix® Jaloskin® Suprathel® Talymed®

Products derived from human donor tissue, minimally processed	Products derived from living human and/or animal tissue	Acellular animal-derived products	Biosynthetic products
		Integra™ Bilayer Matrix Wound Dressing Integra™ Flowable Wound Matrix LTM Wound Dressing MatriStem Matristem Micromatrix® Matristem® Burn Matrix MatriStem® Wound Matrix Matrix Collagen Wound Dressing Medline Collagen Wound Dressing OASIS Burn Matrix™ OASIS Wound Matrix™ Primatrix™ Primatrix™ Dermal Repair Scaffold SIS Wound Dressing II SS Matrix™ Stimulen™ Collagen TheraPorm™ Standard/Sheet Unite® Biomatrix Unite™ Biomatrix	

The following skin substitute products may not be available for chronic wounds in the US: Dermagen, EpiDex, Hyalograft, Kaloderm, Matriderm, PermaDerm, StrataGraft/ExpressGraft, and Xelma.

### Key Questions and Outcomes

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix D.

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
  - a. Age
  - b. Body mass index (BMI)
  - c. Comorbidities
  - d. Site of ulcer
  - e. Ulcer etiology (e.g. infectious, pressure or circulatory).
  - f. Wound severity
  - g. Prior need for skin substitute
  - h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

*Critical outcomes* selected for inclusion in the GRADE table: deep soft tissue or bone infection, complete wound healing, and quality of life. *Important outcomes* selected for inclusion in the GRADE table: time to complete wound healing and adverse effects.

## Evidence overview

Four systematic reviews and two additional RCTs address the use of skin substitutes for chronic skin ulcers; they are summarized in Tables 2 and 3. The outcomes considered critical for purposes of this coverage guidance are deep soft tissue or bone infection, complete wound healing, and quality of life. Time to complete wound healing and adverse effects are considered important outcomes. Complete wound healing is generally defined as “full epithelialization with no drainage, no exudate or eschar (scab) present” (Snyder, Sullivan & Schoelles, 2012, p. 48).

Although some products may have similar components or substrates, “[t]he results obtained from studies of a single product [...] cannot be extrapolated to all products in a group because of differences in product components and healing properties” (Snyder, Sullivan & Schoelles, 2012, p. 48). Therefore, the results are organized by product type below.

Results are also separated by indication (diabetic foot ulcer or venous leg ulcer; the search did not identify any evidence for skin substitutes in the treatment of decubitus ulcers). Effectiveness for one type of wound cannot be extrapolated across indications “because of the difference in etiology and pathophysiology” between different types of wounds (Snyder, Sullivan & Schoelles, 2012, p. 56).

One limitation of the body of evidence is a lack of standardization of comparators. Some trials compare one skin substitute versus another, but many use “usual care” in the control group. Some treatments that fall into the category of usual care can include (but are not limited to):

- Diabetic Foot Ulcers – usual care techniques:
  - Nonadherent gauze dressing (Mepitel), covered with a secondary dressing including saline-moistened gauze and dry gauze

- Saline-moistened, nonadherent gauze (Teapore) covered with a layer of saline-moistened gauze followed by dry gauze and petrolatum gauze layer
- Nonadherent interface + saline moistened gauze
- Saline moistened gauze
- Venous Leg Ulcers – usual care techniques:
  - Tegapore (gauze bolster), zinc oxide-impregnated, paste bandage (Unna boot), and self-adherent elastic wrap
  - Multilayered compression therapy

The body of evidence is also limited in the evidence addressing the considerations in Key Question 1. Where possible, discussion of study inclusion/exclusion criteria are presented.

**Table 2. Summary of Included Systematic Reviews**

<b>Systematic Review (Quality) Total N</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
Game (2015) (Fair) N = 1461	Diabetic foot ulcers: 11 RCTs 1 Cohort 1 Case-control	<ul style="list-style-type: none"> <li>● Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft)</li> <li>● Tissue engineered sheet of fibroblast/keratinocyte co-culture (Graftskin)</li> <li>● Living keratinocytes and fibroblasts (Apligraf®)</li> <li>● Amniotic membrane wound graft (Epifix)</li> </ul>	<ul style="list-style-type: none"> <li>● Complete wound healing</li> <li>● Time to complete wound healing</li> </ul>
Felder (2012) (Fair) N = 2043	Chronic foot ulcers (diabetic, angiopathic, venous stasis, pressure-induced, or infected): 15 RCTs 1 Cohort 5 SRs	<ul style="list-style-type: none"> <li>● Bilayer of neonatal keratinocytes and fibroblasts on hyaluronic acid matrix (Apligraf/Graftskin)</li> <li>● Neonatal fibroblasts and keratinocytes cultured onto bovine collagen matrix (OrCel)</li> </ul>	<ul style="list-style-type: none"> <li>● Complete wound healing</li> <li>● Time to complete wound healing</li> <li>● Infection rate</li> <li>● Complications</li> <li>● Ulcer recurrence</li> </ul>

<b>Systematic Review (Quality) Total N</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
		<ul style="list-style-type: none"> <li>• Cryopreserved split-thickness skin allograft (TheraSkin)</li> <li>• Allogeneic fetal fibroblasts on polyglactic matrix (Dermagraft)</li> <li>• Autologous cultured keratinocytes on hyaluronic acid-derived, perforated lamina (Laserskin)</li> <li>• Decellularized cadaveric dermis (Graftjacket®)</li> <li>• Bovine collagen and chondroitin-6-sulfate scaffold with silicone covering (Synthetic Integra)</li> </ul>	
Jones (2013) (Good) N = 438	Venous leg ulcers: 5 RCTs	<ul style="list-style-type: none"> <li>• Allogenic bilaminar Composite Cultured Skin (OrCel™)</li> <li>• Cultured epidermal allograft (Autoderm™)</li> <li>• Products derived from live human/animal tissue (Apligraf®, Dermagraft®)</li> </ul>	<ul style="list-style-type: none"> <li>• Complete wound healing</li> <li>• Time to complete healing</li> <li>• Rate of change in ulcer area</li> <li>• Pain</li> <li>• Adverse events</li> </ul>
Snyder (2012) (Good) N = 1,829	Diabetic foot ulcers: 12 RCTs Vascular leg ulcers: 6 RCTs	<ul style="list-style-type: none"> <li>• Products derived from human donor tissue (Graftjacket®)</li> <li>• Products derived from live human/animal tissue (Apligraf®, Dermagraft®)</li> </ul>	<ul style="list-style-type: none"> <li>• Wound infection</li> <li>• Complete wound healing</li> <li>• Time to complete wound healing</li> </ul>

<b>Systematic Review (Quality)</b>	<b>Population No. and Type of Included Studies</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
<b>Total N</b>		<ul style="list-style-type: none"> <li>• Acellular animal derived products (OASIS® Wound Matrix)</li> <li>• Biosynthetic products (Talymed®)</li> </ul>	<ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Quality of life surrogate outcomes (return to baseline activities of daily living and function, pain reduction)</li> </ul>

**Table 3. Summary of Included Randomized Controlled Trials identified in additional Medline search**

<b>RCT (Quality)</b>	<b>Population</b>	<b>Skin Substitute Category</b>	<b>Outcomes of Interest</b>
<b>Total N</b>			
Lavery 2014 (Poor) N = 97	Diabetic foot ulcers	<ul style="list-style-type: none"> <li>• Placenta-derived human viable wound matrix (Grafix®)</li> </ul>	<ul style="list-style-type: none"> <li>• Complete wound healing</li> <li>• Time to complete healing</li> <li>• Adverse events</li> <li>• Wound-related infections</li> </ul>

## EVIDENCE SUMMARY

*Snyder [AHRQ] (2012)*

The AHRQ systematic review by Snyder, Sullivan and Schoelles (2012) included 18 RCTs (12 on DFUs, 6 on VLUs). Of the 18 studies, eight were assessed as a low risk of bias, nine as a moderate risk of bias, and one with an unclear risk of bias. The review authors limited study inclusion to RCTs that had a minimum of 10 patients per treatment arm. In addition to the outcomes described in Table 1, the AHRQ review evaluated wound recurrence, need for amputation, need for hospitalization, return to baseline activities of daily living and function, pain reduction, and exudate and odor reduction.

### *Felder (2012)*

The systematic review by Felder, Goyal, and Attinger (2012) included 15 RCTs and one prospective cohort study as well as five systematic reviews. This SR was concerned with chronic foot ulcers of any origin. There is significant overlap in included studies (nine RCTS) between the AHRQ SR (Snyder, Sullivan and Schoelles, 2012) and this SR. Felder and colleagues (2012) included five additional studies (3 DFU, 1 VLU, 1 non-healing foot ulcer) that were not included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of these five, one was assessed at low risk of bias, one at moderate risk of bias, and three at high risk of bias. Rate of complete wound healing was the primary outcome; secondary outcomes included time to complete wound healing, infection rates, and ulcer recurrence.

### *Jones [Cochrane] (2013)*

The Jones systematic review (Jones, Nelson and Al-Hity, 2013) focused on the treatment of VLUs and included five RCTs on the use of skin substitutes, two of which overlap with the AHRQ review (Snyder, Sullivan and Schoelles, 2012). Of the remaining three studies, one is rated as unclear risk of bias, one at low risk of bias, and one at moderate risk of bias. Authors included any randomized study, regardless of publication status or language, in which skin grafts or skin replacements for venous leg ulcers were compared against any other intervention (only studies involving skin substitutes are summarized in this coverage guidance), and which reported on the primary outcomes of wound healing, time to complete healing, or absolute rate of change of ulcer area.

### *Game (2015)*

A systematic review by Game and colleagues (2015) assessed the effectiveness of various interventions for diabetic foot ulcers. This is the second update of a systematic review undertaken by the International Working Group of the Diabetic Foot (IWGDF) in 2006 and first updated in June 2010. Game and colleagues (2015) included all controlled studies, both prospective and retrospective, that evaluated treatment of chronic foot ulcers in adults (age 18 and older) with type 1 or type 2 diabetes. Primary outcomes were healing, time to healing, and reduction in wound area. The 2015 review included 11 RCTs relevant to skin substitutes; all but three of them overlap with the other SRs included in this report. Of those three, one was rated at medium risk of bias and the others at high risk of bias.

## **Apligraf® / Graftskin**

Apligraf®, known previously as Graftskin, is a “living cell based bilayered skin substitute derived from bovine type 1 collagen and human fibroblasts and keratinocytes derived from neonatal foreskins” (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The FDA has approved Apligraf®

For use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment

of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.

Apligraf is contraindicated for use on clinically infected wounds. Apligraf is contraindicated in patients with known allergies to bovine collagen. Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium." of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks' duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure (Snyder, Sullivan, and Schoelles, 2012, pg 38).

The prescribing information contains a caution; "The safety and effectiveness of Apligraf have not been established for patients receiving greater than 5 device applications."

Inclusion criteria for trials of Apligraf<sup>®</sup> varied in the size and severity of wounds. Minimum duration was 2-4 weeks. Patients were excluded for conditions that would impair wound healing such as poor glycemic control (identified in one trial as hemoglobin A1c  $\geq 12$ ), active infection, immunocompromise (either from underlying disease, radiation, chemotherapy, or recent corticosteroid use), evidence of skin cancer at or near the wound, renal or hepatic impairment, drug or alcohol abuse, and Charcot foot or inability to offload the ulcer. Some studies excluded patients whose ulcers responded to usual care in a 7-14 day run-in period. The majority of patients were male and in their 50s or 60s.

Three early studies (Sabolinski, 1996; Falanga, 1998; Falanga & Sabolinski, 1999) all used the same protocol of up to five applications within the first 21 days of treatment. Ulcers were re-examined every few days and if less than 50% of the previous application "took," researchers applied the product again, up to five times in total. The earliest study reported that 70% of patients got 1-3 grafts; the others did not report how many applications were required. A 2009 study re-examined patients at 4 and 8 weeks after initial application and re-applied as necessary. "In the Apligraf group, 13 of the 33 subjects required only 1 application of Apligraf, and 15 and 5 subjects received 2 or 3 applications, respectively. On average, subjects received 1.8 Apligraf applications during the course of the study" (Edmonds, 2009, pg. 14). The comparative study of Apligraf<sup>®</sup> vs TheraSkin<sup>®</sup> (DiDomenico, 2011) put no limits on the number of applications and allowed them at clinician discretion, they report an average of 1.53 applications (SD = 1.65).

Chang, 2000 used only a single application for all subjects, and reported on costs thusly:

At our institution, professional fee reimbursement for all skin graft procedures averages \$1 350. A single 7-inch disk of Apligraf costs \$1000 to the third-party insurer or the patient. The reimbursement for a 3- to 5-day hospital stay, including operating room and recovery room costs, average \$8000-\$11,000 for a Medicare patient. Therefore, Apligraf application in these patients costs \$7000 to \$10,000 less than an autologous skin graft. Moreover, further cost reductions may be possible as demand for this product increases. Finally, wound closure yields may further be improved with multiple applications of TEGS and as the optimal dressing and management of TEGS-treated wounds in this patient population become better defined (Chang, 2000, pg. 49).

#### *Critical Outcome: Deep Soft Tissue or Bone Infection*

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one trial that reported cases of osteomyelitis in patients with DFUs treated with either Apligraf®/Graftskin or usual care. The RCT compared Apligraf® to saline-moistened gauze (treatment group, n = 112; usual care group, n = 96). There was a significantly lower incidence of osteomyelitis in the Apligraf® group compared to usual care (2.7% vs 10.4%, p = 0.04).

For VLU, the AHRQ review included a single RCT comparing Apligraf® to compression therapy (treatment group, n = 161; usual care group, n = 136) that reported incidence of osteomyelitis. Approximately eight percent of patients receiving Apligraf® developed osteomyelitis at the study site, compared with no patients in the comparison group developing a bone infection (no statistical analysis conducted).

#### *Critical Outcome: Complete Wound Healing*

Snyder and colleagues (2012) included three RCTs comparing Apligraf® to usual care. Two of the trials included patients with DFUs (total n = 280) and the third trial focused on VLUs (n = 275). The AHRQ review (Snyder, Sullivan and Schoelles, 2012) found the use of Apligraf® was associated with significantly greater percentage of wound closures compared to usual care for patients with DFUs at 12 weeks (Trial 1, n=72, 52% vs 26%, p=0.03, relative risk 1.96, 95% CI 1.05 to 3.66; Trial 2, n=208, 56% vs 38%, p=0.01, relative risk 1.5, 95% CI 1.11 to 2.04) and patients with VLUs at 12 weeks (53% vs 22%, p<0.001, relative risk 2.38, 95% CI 1.67 to 3.39).

Felder and colleagues (2012) included two additional RCTs comparing Apligraf® to usual care. The first was a subgroup analysis of a larger study which looked at 120 patients whose ulcers had been present for at least one year, comparing Apligraf® to multilayer compression wrap. In this hard-to-heal subgroup, complete healing occurred by six months in 47% of subjects receiving Apligraf® versus 19% of the control subjects. The second study included by Felder (2012) compared Apligraf® against saline gauze dressing in patients with chronic foot ulcers of any etiology who had undergone limb revascularization within 60 days. Complete closure by six months occurred in 100% of Apligraf® patients, compared to 75% of usual care patients (p < 0.01).

## Apligraf® vs Theraskin®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Apligraf® and Theraskin® for DFUs (n = 28). Average wound size was similar between groups. There were no significant differences reported in complete wound closure between the two products (Apligraf® 41% vs Theraskin® 67%, p=0.21).

### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of Apligraf® on validated quality of life indicators. One RCT included in the AHRQ review reported on pain, noting that it improved significantly in both Apligraf® and control groups (Snyder, Sullivan and Schoelles, 2012).

### *Important Outcome: Time to Complete Wound Healing*

Snyder and colleagues (2012) included one RCT that reported on the time to complete wound healing in the use of Apligraf® for VLU. In the single RCT, patients who received Apligraf® experienced shorter median time to wound closure (61 days) compared with usual care (i.e., Unna boot) (191 days).

Felder and colleagues (2012) included one RCT of patients with chronic foot ulcers who had recently (60 days) undergone limb revascularization, which found mean time to healing with Apligraf® was seven weeks, compared to 15 weeks in the group treated with saline-gauze dressing (p = 0.0021).

### *Important Outcome: Adverse Effects*

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included four studies that reported on adverse effects from Apligraf® for a total of 332 patients treated with the product and 283 patients treated with usual care. Two RCTs (N = 28 and N = 72) reported only “serious adverse events” in the treatment and follow-up phases, and these were roughly equivalent (3-5 patients in each group). One trial only reported on osteomyelitis, which is discussed above. In the fourth RCT (N = 297), there were approximately equal incidences of cellulitis (15.5% vs 13.2%), dermatitis (8.7% vs 8.8%), and peripheral edema (5.0% vs 5.0%) in the Apligraf® group compared to usual care.

Although not explicitly stated as a critical outcome, one trial reported on the incidence of death. Six cases of death reported in the Apligraf® group compared with five cases in the usual care group (reasons not described); there were no other deaths reported across the three other trials.

Felder and colleagues (2012) included one additional study (a subgroup of a previous study, separating out 120 patients with hard-to-heal venous ulcers present longer than one year) that reported infection rates of 8.2% in the Apligraf® treatment group (n = 72) versus 7.8% in the usual care control group (n = 48).

In addition to the adverse effects described above, trials also reported relatively rare incidence of rashes, pain, urinary tract infection, pain, dyspnea, congestive heart failure, accidental injury, pharyngitis, asthenia, arrhythmia, arthralgia, increased cough, erythema, and kidney failure.

## **Dermagraft®**

Dermagraft® is a “cryopreserved human fibroblast-derived dermal substitute on a bioabsorbable polyglactin mesh scaffold. The fibroblasts are obtained from human newborn foreskin tissue” (Snyder, Sullivan and Schoelles, 2012, pg 38). It is indicated by the FDA

[f]or use in the treatment of full-thickness diabetic foot ulcers greater than six weeks’ duration which extend through the dermis, but without tendon muscle, joint capsule or bone exposure. Dermagraft® should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot. Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Dermagraft is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution (Snyder, Sullivan and Schoelles, 2012, pg 38).

The FDA prescribing information contains a caution that Dermagraft has not been studied in patients receiving greater than 8 device applications.

Trials of Dermagraft® included patients with adequate glycemic control and evidence of adequate circulation as measured by ankle brachial pressure index (ABPI). Patients were excluded for evidence of active infection, impaired mobility, and significant comorbidities such as HIV, severe peripheral vascular disease, or a bleeding disorder. Patients were also generally excluded if their ulcers responded to usual care during a run-in or screening period. Average age ranged from 55 to 72 years.

Application regimens for Dermagraft® are diverse in the literature. Earlier trials involved weekly applications for up to 7 or 8 treatments (Gentzkow, 1996; Naughton, 1997; Marston, 2003). A study in 2003 divided patients into three different treatment arms; weekly applications for up to 12 weeks and a total of four applications at 0, 1, 4, and 8 weeks had identical efficacy (5/13 wounds healed). The most recent trial in this report (Omar, 2004) used this same 0, 1, 4, and 8 protocol and had a similar result (5/10 ulcers healed).

#### ***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT comparing Dermagraft® to saline-moistened gauze in the treatment of DFU that reported on incidence of osteomyelitis. Rates were 8.6% in both the intervention and the control groups.

#### ***Critical Outcome: Complete Wound Healing***

Snyder and colleagues (2012) included three RCTs that reported on complete wound healing in the use of Dermagraft® for DFUs. All three RCTs on DFUs found that patients receiving Dermagraft® experienced greater rates of complete wound healing compared to usual care at 12 weeks. A meta-analysis found Dermagraft to be more effective for achieving wound closure compared to usual care (saline-moistened gauze) for patients with DFUs (odds ratio 1.64; 95% CI 1.10 to 2.43).

Felder and colleagues (2012) identified one additional RCT of Dermagraft® in care of DFUs, in which the metabolic activity of the graft was assessed and patients in the treatment arm were stratified by whether or not the Dermagraft® was “metabolically active within the therapeutic range” (Felder, 2012, p. 150). At twelve weeks, the rate of complete healing was 38.5% in the entire treatment group and 31.7% in the control group (p = 0.138), but was 50.8% in the “metabolically active” Dermagraft® group.

Snyder and colleagues (2012) identified one RCT that included patients with VLUs, which found greater rates of complete wound healing in the Dermagraft® group at 12 weeks, although this finding was not statistically significant (28% vs 15%, p=0.30, relative risk 1.83, 95% CI 0.47 to 7.21).

Jones and colleagues (2013) identified one additional RCT of Dermagraft® versus usual care in VLUs that used a four-piece protocol. They pooled this data with the results of the aforementioned RCT and found that “There was no evidence of overall benefit associated with four pieces of dermal skin replacement (at baseline, one, four and eight weeks) in the two studies (RR 3.04, 95% CI 0.95 to 9.68), when pooled using a fixed-effect model (44 participants)” (Jones, Nelson, and Al-Hity, 2013, p. 10).

#### Dermagraft® vs OASIS®

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). Average wound size was similar between groups (p = 0.94). There were no significant differences reported in complete wound closure between the two products (Dermagraft 84.6% vs OASIS® 76.9%, p = 0.62).

#### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of Dermagraft® on validated quality of life indicators or surrogate measures.

#### *Important Outcome: Time to Complete Wound Healing*

Felder and colleagues (2012) identified four RCTs that reported on time to complete healing for DFUs treated with Dermagraft®. In all four trials, generally speaking, healing was faster in the Dermagraft® group than in the control. A fair quality small RCT testing three different Dermagraft® regimens against usual care (N=50) found that weekly application of Dermagraft® resulted in mean time to healing of 12 weeks, while less frequent applications and usual care led to healing times greater than 12 weeks. A second, fair quality RCT (N=235) assessed the metabolic activity of the Dermagraft® product prior to application and found an improvement in healing time (13 weeks vs 28 weeks) only when the product was “metabolically active within the therapeutic range” (Felder, Goyal, and Attinger, 2012, p. 150). A poor quality RCT (N=281) published the same year had identical results (13 weeks vs 28 weeks), while the final RCT in this review (also poor quality, N=245) demonstrated that time to healing was significantly faster with Dermagraft than with control (p = 0.04)

Similarly, the one RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) on the use of Dermagraft® for patient with VLUs found shorter wound closure time in the Dermagraft group compared with usual care (35 weeks vs 74 weeks).

## **Dermagraft® vs OASIS®**

One RCT included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) evaluated the comparative effectiveness of Dermagraft® and OASIS® for DFUs (n = 26). There were no significant differences reported in complete wound closure between the two products (Dermagraft 40.90 ± 32.32 days vs OASIS® 35.67 ± 41.47 days, p = 0.73).

### *Important Outcome: Adverse Effects*

Two trials identified by Felder and colleagues (2012) reported on adverse effects with Dermagraft®. One trial (n = 314) found that compared to usual care (saline-moistened gauze), patients who received Dermagraft® had lower rates of adverse effects (i.e., infection, osteo and cellulitis) (19% vs 32%, p=0.007). In the second trial, patients in the Dermagraft® groups had similar rates of adverse events (undefined, statistical significance not reported in the AHRQ review). Unrelated AEs in this study (N = 53) included syncope, skin excoriation, bleeding from biopsy site, latex allergy, development of bullous pemphigoid, and cerebrovascular accident.

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported adverse events from one fair quality RCT (N=53) of Dermagraft® in treatment of VLU. With 13-14 subjects in each treatment group, total number of adverse events was 15-18 per group, Serious adverse events were not reported in the control group; the three treatment groups each had at least one serious adverse event, with four serious events in the most intensive treatment arm.

## **EpiFix®**

EpiFix® is derived from human amniotic membrane and is marketed both in a skin allograft form as well as an injectable form. It does not presently have any FDA indications. This evidence review identified one small RCT of EpiFix®. Patients were 56-62 years old, were 69% and 58% male in the intervention and control groups, respectively, and had ulcers averaging 2.8cm<sup>2</sup> in the intervention group and 3.4 cm<sup>2</sup> in the controls. Other inclusion/exclusion criteria were not described and significance of baseline differences were not reported.

In this RCT (Zelen, 2013), patients who had incomplete epithelialization received an additional application at weeks 2, 4, 6, 8, and 10. The authors state, "Five patients (45%) healed with one dHAM application, one (9.1%) healed with two applications, one (9.1%) healed with three applications, two (18%) healed with four applications, and one (9.1%) healed after five applications." This is an average of 2.3 applications.

### *Critical Outcome: Deep Soft Tissue or Bone Infection*

No SRs or RCTs reported on the effect of EpiFix® on deep soft tissue or bone infection.

### *Critical Outcome: Complete Wound Healing*

Game and colleagues (2015) identified one RCT of EpiFix®, an amniotic membrane graft product, in the treatment of DFUs. This was a small pilot study in which 13 patients with an average wound size of 2.8

cm<sup>2</sup> were treated with EpiFix<sup>®</sup> and 12 patients with an average wound size of 3.4 cm<sup>2</sup> were treated with moistened gauze and silver; all patients received compression dressings. At four weeks, complete healing was 77% in the EpiFix<sup>®</sup> group and 0% in the control group ( $p < 0.0001$ ). By six weeks, rates of complete healing were 92% and 8%, respectively ( $p < 0.0001$ ). This is an unexpectedly low rate of healing in the control group.

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of EpiFix<sup>®</sup> on validated quality of life indicators or surrogate measures.

***Important Outcome: Time to Complete Wound Healing***

No SRs or RCTs reported on the effect of EpiFix<sup>®</sup> on time to complete wound healing.

***Important Outcome: Adverse Effects***

No SRs or RCTs reported on the adverse effects of EpiFix<sup>®</sup>.

## **Grafix<sup>®</sup>**

Grafix<sup>®</sup> is another product derived from cryopreserved human placental membrane. It is approved by the FDA as a “wound cover” for both acute and chronic wounds. According to the manufacturer it intends to submit a Biologics License Application for more clinical indications. This evidence review identified only one RCT of poor quality. Patients in this trial had wounds of four to 52 weeks’ duration, and of one to 15 cm<sup>2</sup> in area. Patients were excluded for A1c  $\geq 12$ , inadequate ABPI, presence of active infection, and response to usual care during a one-week screening period. Other subject characteristics were not reported. Patients received weekly applications for up to 84 days (Lavery, 2014).

***Critical Outcome: Deep Soft Tissue or Bone Infection***

No SRs or RCTs reported on the effect of Grafix<sup>®</sup> on deep soft tissue or bone infection. The RCT by Lavery and colleagues (2014) did report that patients randomized to Grafix<sup>®</sup> did experience significantly fewer wound infections than the usual-care group (18.0% versus 36.2%,  $p = 0.044$ ), and a trend to fewer infection-related hospitalizations (6% versus 15%,  $p = 0.15$ ).

***Critical Outcome: Complete Wound Healing***

Lavery and colleagues (2014) conducted an RCT of Grafix<sup>®</sup> versus standard wound care for DFUs. Patient groups were similar at baseline. Complete wound healing occurred in 62% of patients treated with Grafix<sup>®</sup> and in 21% of the control group ( $p < 0.01$ ). The quality of this study is poor due to having no description of randomization methodology, nor concealment or blinding efforts. The study was funded by manufacturer.

***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of Grafix<sup>®</sup> on validated quality of life indicators or surrogate measures.

### ***Important Outcome: Time to Complete Wound Healing***

In the poor quality RCT by Lavery and colleagues (2014), time to complete healing was a secondary outcome. Patients treated with Graftix<sup>®</sup> experienced complete wound healing in a median time of 42 days, compared to 69.5 days in the control group ( $p = 0.019$ ).

### ***Important Outcome: Adverse Effects***

Lavery and colleagues (2014) reported that patients treated with Graftix<sup>®</sup> were less likely to experience any adverse event than patients in the control group (44% versus 66%,  $p = 0.031$ ). One control group subject underwent amputation due to an adverse event; there were no amputations in the intervention arm. There was no discussion of whether any of the adverse events were thought to be related to treatment.

## **Graftjacket<sup>®</sup>**

Graftjacket<sup>®</sup> is derived from donated human tissue, and is composed of extracellular components of human dermis (collagen, elastin, and proteoglycans). One RCT included patients with non-infected ulcers and a palpable/audible pulse to the affected extremity, but did not describe other inclusion/exclusion criteria. A second RCT included only patients with good diabetic control (Hgb A1c < 12, serum creatinine < 3.0 mg) and adequate ABPI, and excluded patients who had received biomedical or topical growth factors within 30 days. Other subject characteristics were not reported. Both RCTs used a single application in the treatment group (Brigido, 2006; Reyzelman, 2009).

### ***Critical Outcome: Deep Soft Tissue or Bone Infection***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT that reported wound infection rates in the use of Graftjacket<sup>®</sup>. In 46 patients treated with Graftjacket<sup>®</sup>, one patient experienced a wound infection that eventually ended with amputation; there were no cases of wound infection in the 39 control group subjects.

### ***Critical Outcome: Complete Wound Healing***

Two RCTs were included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated the use of Graftjacket<sup>®</sup> in patients with DFUs (total  $n = 113$ ). The authors of both studies report a significantly greater proportion of wound closure compared to usual care at 12 weeks (compared with moist-wound therapy dressings: 70% vs 46%,  $p=0.03$ , relative risk 1.51, 95% CI 1.02 to 2.22; compared with Curasol: 86% vs 29%,  $p=0.006$ ). In the AHRQ review, one of these RCTs was assessed at moderate risk of bias; the other was determined to be at low risk of bias after author communications clarified the randomization procedures. However, Felder and colleagues (2012) point out other flaws in this second RCT, specifically that the dropout rate was twice as high in the treatment group as in the control group, that the average pretreatment wound size was biased in favor of the Graftjacket arm ( $3.6\text{cm}^2$  in the treatment subjects versus  $5.1\text{cm}^2$  in the control subjects), and that the control group “had a higher percentage of foot wounds, which are more likely to be weight-bearing and therefore more difficult to heal” (Felder, Goyal and Attinger, 2012, p. 60).

### ***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of Graftjacket® on validated quality of life indicators or surrogate measures.

### ***Important Outcome: Time to Complete Wound Healing***

The AHRQ SR (Snyder, Sullivan and Schoelles, 2012) included two RCTs that reviewed the effectiveness of Graftjacket for DFUs. In one trial, time to complete healing was 11.92 weeks in the treatment group versus 13.5 weeks in the control group; in the other, it was 5.7 weeks in the treatment group versus 6.8 weeks in the control. While both studies reported a shortened time to wound closure compared to a usual care group, neither finding was statistically significant.

### ***Important Outcome: Adverse Effects***

One RCT reported wound infection rates of 21.4% versus 35.7% in the treatment and control groups, respectively (Felder, Goyal and Attinger, 2012). The other RCT reported on a control group patient who experienced altered mental status and hypotension and another who developed an abscess; in the treatment group, one patient had an infection leading to amputation (discussed above), and a second required vascular surgery.

## **OASIS® Wound Matrix**

OASIS® is derived from hydrolyzed bovine collagen and is approved by the FDA “[f]or the management of wounds including full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, second-degree burns, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical incisions” (Snyder, Sullivan and Schoelles, 2012, pg. ES-12). The AHRQ review identified five RCTs evaluating the effectiveness of OASIS®. Patients were enrolled with a wound of >4 weeks duration (in one trial, > 6 months). Patients with conditions that would slow wound healing were excluded from all trials, for example, malnutrition (albumin < 2.5 g/dL), poor glycemic control (A1c >12), active smoker status, inadequate circulation to the affected limb, active infection, immunosuppression, use of steroids, vascular disease, and Charcot foot.

In three trials of OASIS<sup>®</sup> for DFU, the product was re-applied as deemed clinically necessary. One RCT (Niezgoda, 2005) reported an average use of 10 sheets of OASIS per patient. A trial of OASIS compared to Dermagraft<sup>®</sup> (Landsman, 2008) reported that up to eight applications of OASIS was similarly effective to up to three applications of Dermagraft<sup>®</sup>. The third trial (Romanelli, 2010) reported an average of 5.2 days between dressing changes for OASIS patients.

Two RCTs reported on OASIS<sup>®</sup> in treatment of VLU. One (Mostow, 2005) reported an average of eight sheets per patient; the other (Romanelli, 2007) reported an average of 6.4 days between dressing changes but did not report on number of sheets of product used.

***Critical Outcome: Deep Soft Tissue or Bone Infection***

No SRs or RCTs reported on the effect of OASIS<sup>®</sup> on deep soft tissue or bone infection.

***Critical Outcome: Complete Wound Healing***

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included one RCT of patients with DFUs (n = 98), comparing OASIS<sup>®</sup> Wound Matrix with Regranex Gel (contains platelet-derived growth factor) and found greater wound closure of plantar ulcers at 12 weeks in the OASIS<sup>®</sup> group (49% vs 28%, p=0.06).

[A second RCT comparing OASIS<sup>®</sup> Wound Matrix with standard care was identified after the initial search and draft coverage guidance was completed. Cazzell and colleagues \(2015\) published results of an open-label RCT of 82 patients comparing OASIS<sup>®</sup> to standard care for treatment of DFU. In the intervention group, OASIS was applied once each week. Patients in the control group were also seen weekly and the standard care intervention was selected by the investigator \(standard care included silver dressing, Hydrogel, wet-to-dry, alginate, Manuka honey, or triple antibiotic dressing\). Ulcer measurement was standardized by use of a digital image capture and wound measurement device. At 12 weeks, wound healing was greater in the OASIS group \(54%\) compared with the standard care group \(32%\) \(p=0.021\). Smith and Nephew funded the study and employs three of the authors. Aside from the conflicts of interest and open-label design, the study otherwise appears to be at low risk of bias. This fair quality RCT demonstrates improved DFU wound healing at 12 weeks for patients treated with OASIS compared to standard care.](#)

Snyder and colleagues (2012) included three RCTs of patients with VLUs that evaluated the effectiveness of OASIS<sup>®</sup> Wound Matrix (total n = 222). The trials included disparate usual care groups (petrolatum-impregnated gauze with no compression, Jaloskin containing hyaluronan, nonadherent dressing with compression bandages). However, healing rates were greater in the OASIS<sup>®</sup> Wound Matrix arms across all three trials and follow-up periods (80% vs 65% at 8 weeks, p<0.05; 83% vs 46% at 16 weeks, p<0.001; 55% vs 34% at 12 weeks, p=0.02; respectively).

### OASIS® Wound Matrix vs Dermagraft®

The AHRQ SR included one RCT that compared OASIS® Wound Matrix with Dermagraft® for individuals with DFUs (n = 26) (Snyder, Sullivan and Schoelles, 2012). The study found no significant difference in the percentage of wound closure between the two products (Dermagraft 84.6% vs OASIS® 76.9%, p = 0.62).

#### ***Critical Outcome: Quality of Life***

No SRs or RCTs reported on the effect of OASIS® on validated quality of life indicators. One RCT identified in the AHRQ review reported fewer wound dressings with OASIS® (6.46 ± 1.39 changes vs 2.54 ± 0.78), while a second reported lower pain levels in the intervention group as measured by a 10-point visual analog scale (3.7 vs 6.2, p < 0.05). A third RCT reported that 2/17 patients in the OASIS® group experienced pain, compared to 1/10 control patients.

#### ***Important Outcome: Time to Complete Wound Healing***

Of the three RCTs included in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) that evaluated OASIS® Wound Matrix in patients with DFUs, only one trial reported a shorter time to wound closure compared to nonadherent dressing with compression bandages (5.4 weeks vs 8.3 weeks, statistical analysis not reported). A second RCT reported 35.67 ± 41.47 days in the OASIS® arm vs 40.90 ± 32.32 days in the control (not significant). The third RCT reported average time of 67 days with OASIS® and 73 days with control (p = 0.245). All three RCTs were of fair quality.

One RCT of OASIS® in VLU did not report time to healing, but did estimate using Cox analysis that at twelve weeks, 63% of the treatment group vs 29% of the controls would be expected to achieve complete wound healing (Snyder, Sullivan and Schoelles, 2012).

### OASIS® Wound Matrix vs Dermagraft®

The AHRQ SR included one RCT that compared OASIS® Wound Matrix with Dermagraft for individuals with DFUs. The study found no significant difference in the time to wound closure between the two products (Snyder, 2012).

#### ***Important Outcome: Adverse Effects***

The AHRQ SR included one RCT that compared OASIS® with Regranex growth gel (Snyder, Sullivan and Schoelles, 2012). The authors reported adverse effects in the OASIS® group (n=17) including one patient with depression/mood disorder, one patient with gastrointestinal disorder, and three patients with infections in a non-study ulcer. In the Regranex group (n=10), there was one instance of infection in a non-study ulcer, two cases of limb injury, one respiratory tract infection, one case of septic arthritis, and one skin injury.

The AHRQ SR also reported on one trial in which eight patients received OASIS® and 15 were treated with compression. In this trial, three patients in each group experienced an allergic reaction or intolerance to the secondary dressing. One patient in the OASIS® group died of cardiovascular disease;

one patient in the compression group developed a new ulcer from the compression. One patient in each group developed an infection in another (non-target) wound, one patient receiving compression developed a seroma, and one patient in each group suffered skin injury.

## Talymed®

Talymed® is a wound dressing product containing poly-N-acetyl glucosamine (pGlcNAc) derived from microalgae. (Snyder, Sullivan and Schoelles, 2012, pg. 56). This evidence review identified one small pilot RCT within the AHRQ review. Patients in this trial were 59-63 years old, 25-65% male, and had wounds ranging from 2.7 to 3.6 months duration. Patients in both intervention and control groups had comorbidities including hypertension, diabetes, obesity, arthritis, and blood clotting disorders. Patients were excluded for a variety of more severe indications such as collagen vascular disease, Charcot disease, previous radiation, current hemodialysis, or insufficient ABPI.

The RCT (Kelechi, 2011) included three treatment arms (single application, application every other week, or application every three weeks). Weekly application was equivalent to control (45%, n = 9 of 20). Complete healing occurred in 86.4% (n = 19 of 22) and 65.0% (n = 13 of 20) with applications every two and every three weeks, respectively. P-value was significant for every other week versus standard care ( $p < 0.01$ ).

### *Critical Outcome: Deep Soft Tissue or Bone Infection*

No SRs or RCTs reported on the effect of Talymed® on deep soft tissue or bone infection.

### *Critical Outcome: Complete Wound Healing*

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) included a single RCT that evaluated the use of Talymed® in combination with usual care compared to usual care alone for VLU (n=82). Patients receiving Talymed® with usual care every other week experienced higher wound closure rates than usual care alone at 20 weeks (86% vs 45%,  $p=0.0005$ ). Snyder and colleagues (2012) note that patients receiving Talymed® once every three weeks or only receiving one application did not experience statistically significant results.

### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of Talymed® on validated quality of life indicators or surrogate measures.

### *Important Outcome: Time to Complete Wound Healing*

No SRs or RCTs reported on the effect of Talymed® on time to complete wound healing.

### *Important Outcome: Adverse Effects*

In the AHRQ review (Snyder, Sullivan and Schoelles, 2012), a single RCT reported “no pain, edema, or significant treatment-related adverse events occurred” (p. C-65).

## TheraSkin®

TheraSkin® is a cryopreserved human skin allograft (Snyder, Sullivan and Schoelles, 2012). This evidence review identified one RCT in which TheraSkin® was used as a comparison for Apligraf® for diabetic foot ulcers, discussed above. Patients in this trial had either Type I or Type II diabetes with A1c < 12.0 and the ability to comply with an offloading regimen as well as adequate ABPI (>0.75) and absence of infection, gangrenous tissue, or abscess. The study was rated at moderate risk of bias.

Patients in the RCT (DiDomenico, 2011) received up to five applications, in accordance with the manufacturer's recommendations. Authors report that most patients received only a single application and that the mean number of applications was 1.38 (SD = 0.29).

### *Critical Outcome: Deep Soft Tissue or Bone Infection*

The AHRQ review (Snyder, Sullivan and Schoelles, 2012) identified one RCT in which TheraSkin® was used as the comparator to Apligraf®. In this trial, one patient treated with TheraSkin® was hospitalized due to infection, but no further information is available.

### *Critical Outcome: Complete Wound Healing*

The RCT identified in the AHRQ review (Snyder, Sullivan and Schoelles, 2012) reported complete wound healing at two time points. By 12 weeks follow up, the TheraSkin® group had 66.7% complete healing, versus 41.3% in the Apligraf® group (p = 0.21). The difference was even smaller at 20 weeks, as no more patients in the TheraSkin group experienced complete healing (66.7% vs 47.1%, p not reported).

### *Critical Outcome: Quality of Life*

No SRs or RCTs reported on the effect of TheraSkin® on validated quality of life indicators or surrogate measures.

### *Important Outcome: Time to Complete Wound Healing*

No SRs or RCTs reported on the effect of TheraSkin® on time to complete wound healing.

### **Important Outcome: Adverse Effects**

No SRs or RCTs reported on the adverse effects of TheraSkin®

## Summary of the Evidence

The field of biologic skin substitutes for treatment of chronic skin ulcers such as venous leg ulcers and diabetic foot ulcers is rapidly expanding with a variety of new innovations and products. An AHRQ review in 2012 identified 57 unique products, while this updated search found 73 and there are likely more. Evidence for the effectiveness and safety of these products has not kept pace with their development, however, as this review was only able to find published trials of nine products (available in the US), and none dealing with pressure ulcers. While early tests are promising for these products in the

treatment of serious and occasionally life-threatening wounds, our confidence in the estimates of effectiveness is generally very low. Studies are almost universally limited by small sample size and inconsistency in control groups and what is defined as “usual care.” There is virtually no evidence to illuminate the comparative effectiveness of these products, nor to compare their effectiveness versus other alternative types of wound dressings besides moist saline gauze and compression.

Our key question regarding subgroup analysis (considerations of age, BMI, comorbidities, etc.) went largely unanswered by these studies. Where inclusion/exclusion criteria were reported, in general the patients were predominantly male, between 50-70 years of age, had hemoglobin A1c < 12.0%, had no active infectious process, and had adequate circulation to the extremity as measured by ankle-brachial pressure index (ABPI). Some trials excluded other comorbidities such as immunosuppression.

Most trials did report on the likelihood of complete wound closure, which makes comparison of results across studies possible; however, the limitation is that many studies have a short follow-up time that may miss complete healing that takes place in the usual care group at a later time. The second critical outcome was incidence of deep soft tissue or bone infection; this outcome was not widely reported and could be inferred from some studies only by the occasion of an amputation. No information was identified related to validated quality of life indicators for any of the products, although there is very limited information about pain and number of dressing changes for a few products. Time to complete healing is another outcome considered important to this review. In these early trials, the skin substitutes do appear to reduce time to wound healing but it should be noted that none of the trials had adequate blinding and many are subject to selection as well as observer bias.

In the AHRQ review, Snyder and colleagues (2012) express concern about the external validity of this body of evidence:

The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. Although these results are consistent in showing a benefit when using skin substitutes and suggest that skin substitutes could be used in treating diabetic foot ulcers and venous leg ulcers, the patients enrolled in these studies were in generally good health and free of infected wounds, medications that would impede wound healing, clinically significant medical conditions, significant peripheral vascular disease, malnutrition, or uncontrolled diabetes. The results of these studies may not easily translate to everyday clinical situations. The expected population with chronic wounds is likely to have these conditions; therefore, the results reported in studies without these patients may not extrapolate well. The applicability of the findings to sicker patients may be limited (Snyder, Sullivan and Schoelles, 2012, p. 74).

These products are dissimilar enough that even though they can be broadly categorized by derivation, results from a trial of one product cannot be extrapolated to other products in its category. With such a large number of products, it will be challenging to have high confidence in the evidence of their effectiveness without many, many more trials.

## OTHER DECISION FACTORS –

### Resource Allocation

Cost for a course of treatment with skin substitutes can vary widely, depending on the product used, the number of applications required, the amount of skin substitute purchased, where it is applied (inpatient hospital, outpatient hospital, ambulatory surgical center, office) and payer reimbursement policies.

Costs for a course of treatment can vary from a few hundred dollars for an in-office treatment with a low-cost skin substitute such as OASIS® Wound Matrix to several thousand dollars for multiple applications of higher cost products such as Apligraf and Dermagraft. While these products are sometimes billed separately from the physician fees for applying them (including related debridement), some payers are bundling payment in order to incentivize the use of cost-effective products. For instance, in the ambulatory surgery center setting, Medicare fee for service bundles the professional fee with the product itself. In addition, in a form of reference pricing, Medicare groups these bundles into two groups--for high-cost and low cost products—in order to encourage the use of cost-effective products. Some other payers follow Medicare’s practices, but others have their own reimbursement policies.

When not bundled, prices for the skin substitute product itself are usually based on the number of square centimeters purchased, though some products are only sold in relatively large pieces (creating waste when used for small ulcers), while others can be purchased in a variety of sizes. In addition, some products are perishable and must be ordered to arrive within a few days of use; others have a longer shelf life. If these products are effective at improving time to complete ulcer healing, or preventing amputations, they could be cost-effective. However, given the low quality evidence available on most of these products, it is difficult to determine whether or not the expected improvement is sufficient to justify the cost.

For products recommended for coverage, the GRADE-informed framework above shows examples of pricing for smaller ulcers for Medicare fee-for-service in various settings.

When multiple effective skin substitutes are available for a given indication, strategizing preferred products based on price or using alternative payment strategies may create savings for payers.

### Values and preferences

Ulcers can be painful, distressing, and debilitating to patients and patients would likely be highly motivated to have effective treatment. However, few of these products have any evidence of benefit at this point and patients would be unlikely to strongly prefer skin substitutes if benefit is unclear. Skin substitutes, however, do not appear to add much burden to the patient; they would continue to require frequent wound dressings, offloading, and other mediating treatments regardless of the use of skin substitutes, so adverse effects or impact on convenience would not be a strong consideration against these products.

## Other considerations

Expert input and study inclusion criteria show that skin substitutes can only be effective when other conditions necessary for wound healing exist. These conditions include the following:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable
3. Appropriate offloading has been performed
4. Wound has adequate arterial flow, no ongoing infection and a moist wound healing environment
5. Multilayer compression dressings are used (when clinically appropriate)
6. Patient has not used tobacco products 4 weeks prior to placement
7. For patients with diabetes, Hba1c level is < 12.
8. No prior failure of the same skin substitute for the ulcer being treated
9. Prior appropriate wound care therapy has failed to result in significant improvement of the wound over at least 30 days
10. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, required for coverage of ongoing applications
11. Patients is able to adhere to the treatment plan

## POLICY LANDSCAPE

### Quality measures

No quality measures related to skin substitutes were identified on the National Quality Measures Clearinghouse.

### Payer coverage policies

Among the four private payers reviewed, two payers provide coverage of skin substitute products (Aetna and Cigna) and two payers do not have coverage criteria (Moda and Regence). Washington Medicaid only covers one skin substitute (Theraskin for diabetic foot ulcers) and requires prior authorization. No National Coverage Determinations were identified. However, there are four Local Coverage Determinations (LCDs) that specify coverage of skin substitutes. Two of the LCDs detail specific products covered (L34285 and L34593), while the other two do not (L36377 and L35041). Table 4 summarizes the coverage for skin substitutes to treat diabetic foot ulcers (DFU) and venous leg ulcers (VLU) across payers. None of the skin substitute coverage policies cover decubitus ulcers. All payers reviewed, except the Medicare NCD and Washington Medicaid, cover skin substitutes when a wound has not adequately responded to standard treatments, usually within 30 days. Many coverage policies have additional indications that limit use, such as the ulcer being infection-free (Aetna, L35041, L34593, and L34285), the foot having adequate blood supply (Aetna, Cigna, L 35041, and L34593), and HbA1C <

12% (Cigna). Some payers limit the number of applications of skin substitutes, for example, a maximum of four treatments of Apligraf or Epifix in 12 weeks and wound healing must be present (Cigna), not more than 10 applications per wound (L35041), Apligraf and Epifix limited to five applications (L34593), and Graftjacket is limited to one application (L34285).

**Table 4. Summary of Other Payer Coverage of Skin Substitutes**

Payer	Skin Substitutes						
	Apligraf®	Dermagraft®	Epifix®	Graftjacket®	OASIS®	Primatrix®	Theraskin®
Aetna	DFU, VLU	DFU	X	DFU	DFU, VLU	X	X
Cigna	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU
Washington	X	X	X	X	X	X	DFU w/ authorization
LCD-Alabama (L34285)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	X	DFU, VLU
LCD-Iowa (L34593)	DFU, VLU	DFU	DFU, VLU	DFU	DFU, VLU	DFU, VLU	DFU, VLU
LCD-Delaware (L35041)	DFU, VLU – no specific products identified						
LCD-Florida (L36377)	DFU, VLU – no specific products identified						

Key: X – product is not covered

Abbreviations: DFU – diabetic foot ulcer; LCD – local coverage determination; VLU – venous leg ulcer

## Clinical Practice Guidelines

### *Diabetic foot ulcers*

Three clinical practice guidelines address care for diabetic foot ulcers (Braun, Kim, Margolis, Peters, & Lavery, 2006; NICE, 2011; Registered Nurses' Association of Ontario, 2013). The good-quality National Institute for Health and Care Excellence (NICE) clinical practice guidelines recommend to, “Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service” (2015, p.18). The fair-quality guideline from the Registered Nurses' Association of Ontario and Braun and colleagues (2006) poor-quality update to the Wound Healing Society guideline did not include a recommendation on use of skin substitutes.

### *Venous leg ulcers*

Three clinical practice guidelines address care of venous leg ulcers (AAWC, 2010; Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc., 2011; SIGN, 2010). One good-quality guideline, Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers, and one poor-quality guideline from the Association for the Advancement of Wound Care (AAWC) recommend skin substitutes for non-healing or persistent venous leg ulcers, but do not provide recommendations on the use of specific products. The good-quality SIGN guideline found that there is insufficient evidence on which to base a recommendation for including skin substitutes, or any skin grafting.

#### *Pressure ulcers*

The good-quality Institute for Clinical Systems Improvement (ICSI) guideline recommends that clinicians refer the patient to a wound-focused physician or clinician to select the appropriate skin substitute or other biological application for the treatment of chronic skin ulcers, such as platelet gels, platelet-derived growth factor therapy, or extracellular matrix sheets.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

## APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

### Strong recommendation

**In Favor:** The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

**Against:** The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

### Weak recommendation

**In Favor:** The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

**Against:** The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

### Quality or strength of evidence rating across studies for the treatment/outcome<sup>2</sup>

**High:** The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

**Moderate:** The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

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<sup>2</sup> Includes risk of bias, precision, directness, consistency and publication bias

**Low:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

**Very low:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

## APPENDIX B. GRADE EVIDENCE PROFILE<sup>3</sup>

### Apligraf® / Graftskin

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
DFUs	1	RCT	Low	Unknown	Direct	Precise	None	Low confidence in estimate of effect ●●○○
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	2	RCT	Low	Consistent	Direct	Precise	None	Moderate confidence in estimate of effect ●●●○
VLUs	1	RCT	Low	Unknown	Direct	Precise	None	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								

<sup>3</sup> All GRADE Evidence Profiles in this Appendix are in comparison to usual care.

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Time to Complete Wound Healing</b>								
VLUs	1	RCT	Low	Unknown	Direct	Precise	<i>None</i>	Low confidence in estimate of effect ●●○○
Nonhealing foot ulcers – undefined	1	RCT	High	Unknown	Indirect	Precise	<i>None</i>	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFUs	1	RCT	Low	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Low	Unknown	Direct	Unknown	<i>None</i>	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

## Derma graft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	4	RCTs	Moderate to high	Inconsistent	Direct	Precise	<i>3 RCTs of moderate ROB are consistent, a high-risk RCT had a discrepant result</i>	Low confidence in estimate of effect ●●○○
VLUs	2	RCTs	Moderate	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFUs	4	RCT	Moderate to high	Consistent	Direct	Unknown	<i>None</i>	Low confidence in estimate of effect ●●○○
VLUs	1	RCTs	Moderate	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
								●○○○
<b>Adverse Effects</b>								
DFUs	2	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○
VLUs	1	RCT	Moderate	Unknown	Direct	Unknown		Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

## EpiFix®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFU	1	RCT	Moderate	Unknown	Direct	Precise	None	Very low confidence in estimate of effect ●○○○

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
DFUs	1	RCT	High	Unknown	Direct	Precise	<i>“Wound-related infection” not defined</i>	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	<i>None</i>	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	<i>None</i>	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFU	1	RCT	High	Unknown	Direct	Precise	<i>None</i>	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

## Graftjacket®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	2	RCT	Moderate to high	Consistent	Unknown	Precise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
DFUs	2	RCTs	Moderate to high	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								
DFUs	1	RCT	High	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial

## OASIS® Wound Matrix

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
VLU	3	RCT	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
VLU	3	RCTs	Low to moderate	Unknown	Direct	Imprecise	Effectiveness varied based on type of usual care	Very low confidence in estimate of effect ●○○○
<b>Adverse Effects</b>								

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
VLUs	1	RCT	Low	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○
DFUs	1	RCT	Moderate	Unknown	Direct	Imprecise	<i>None</i>	Very low confidence in estimate of effect ●○○○

Abbreviations: DFU – diabetic foot ulcer; RCT – randomized controlled trial; VLU – venous leg ulcer

# Talymed®

Indication	Quality Assessment (Confidence in Estimate of Effect)							
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
VLU	1	RCT	Low	Unknown	Direct	Imprecise	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
VLU	1	RCT	Low	Unknown	Direct	Unknown	None	Very low confidence in estimate of effect ●○○○

Abbreviations: RCT – randomized controlled trial; VLU – venous leg ulcer

## TheraSkin® versus Apligraf®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
DFUs		RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

## OASIS® versus Dermagraft®

Indication	Quality Assessment (Confidence in Estimate of Effect)							Quality
	No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	
<b>Deep Soft Tissue or Bone Infection</b>								
<i>No evidence identified</i>								
<b>Complete Wound Healing</b>								
DFUs	1	RCT	Moderate	Unknown	Indirect	Unknown	None	Very low confidence in estimate of effect ●○○○
<b>Quality of Life</b>								
<i>No evidence identified</i>								
<b>Time to Complete Wound Healing</b>								
<i>No evidence identified</i>								
<b>Adverse Effects</b>								
<i>No evidence identified</i>								

Abbreviations: RCT – randomized controlled trial; DFU – diabetic foot ulcer

## APPENDIX C. METHODS

### Scope Statement

#### *Populations*

Adults with chronic skin ulcers

Population scoping notes: *Considered limiting scope to diabetic foot ulcers and venous leg ulcers, sacral decubitus ulcers, but decided on the broader definition above, considered burns and other types of wounds*

#### *Interventions*

Skin substitutes

Intervention exclusions: None

#### *Comparators*

Usual care

#### *Outcomes*

Critical: Deep soft tissue or bone infections, complete wound healing, quality of life

Important: Time to complete wound healing, adverse effects

Considered but not selected for the GRADE table: *Cellulitis, sepsis, death, need for surgical management, ulcer recurrence*

#### *Key Questions*

1. What is comparative effectiveness of different types of skin substitutes compared with wound care alternatives for individuals with chronic skin ulcers? Include consideration of:
  - a. Age
  - b. Body mass index (BMI)
  - c. Comorbidities
  - d. Site of ulcer
  - e. Ulcer etiology (e.g. infectious, pressure or circulatory).
  - f. Wound severity
  - g. Prior need for skin substitute
  - h. Failure of prior therapies
2. What adverse events are associated with skin substitutes?
3. What are contraindications to the use of skin substitutes?

### Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “wound,” “ulcer,” “skin substitute,” or “bioengineered skin.” Searches of core sources were limited to citations published after 2005.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Institute for Clinical and Economic Review (ICER)
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the AHRQ report (Snyder et al, 2012). The search was limited to publications in English published after 2011 (the end search date for the AHRQ SR). Using the 2012 AHRQ systematic review as the predominant evidence source, a second MEDLINE® (Ovid) search was conducted to identify any randomized controlled trials published after the search dates of the AHRQ review (2011).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Choosing Wisely
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

### *Inclusion/Exclusion Criteria*

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines. A MEDLINE® search was conducted for randomized control trials published after the AHRQ systematic review.

The AHRQ systematic review (Snyder, Sullivan and Schoelles, 2012) was selected as the base systematic review for this topic based on its comprehensiveness; thus systematic reviews published prior to the

AHRQ review were excluded. In addition, several systematic reviews published more recently than the AHRQ review were excluded because they did not include any additional studies that were not already summarized by the included systematic reviews. These four systematic reviews were excluded because they included only studies that were in the AHRQ systematic review:

Game , F. L., Hinchliffe, R. J., Apelqvist, J., Armstrong, D. G., Bakker, K., Hartemann, A., ... Jeffcoate, W.J. (2012). A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*, 28 Suppl 1:119-41. DOI: 10.1002/dmrr.2246.

Greer , N., Foman, N., Dorrian, J., Fitzgerald, P., MacDonald, R., Rutks, I., & Wilt, T. (2012). Advanced wound care therapies for non-healing diabetic, venous, and arterial ulcers: A systematic review. VA-ESP Project #09-009.. Retrieved from <http://link.springer.com/article/10.1007%2Fs40257-014-0081-9>.

Hankin , C. S., Knispel, J., Lopes, M., Bronstone, A., & Maus, E. (2012). Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *Journal of Managed Care Pharmacy*, 18(5), 375-384. Retrieved from <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15289>.

Iorio, M. L., Shuck, J., Attinger, C. E. (2014). Wound healing in the upper and lower extremities – A systematic review on the use of acellular dermal matrices. *Plastic and Reconstructive Surgery*, 130: 5S-2. DOI: 10.1097/PRS.0b013e3182615703.

The following systematic review was excluded because it only included studies found in the AHRQ systematic review or Jones and colleagues (2013):

Valle , M. F., Maruthur, N. M., Wilson, L. M., Malas, M., Qazi, U., Haberl, E., ... Lazarus, G. (2014). Comparative effectiveness of advanced wound dressings for patients with chronic venous leg ulcers: A systematic review. *Wound Repair and Regeneration*, 22(2), 193-204. DOI: 10.1111/wrr.12151.

Finally, the following systematic review was excluded because it did not provide sufficient detail regarding outcomes reported in trials of skin substitutes:

Braun, L. R., Fisk, W. A., Lev-Tov, H., Kirsner, R.S., & Isseroff, R. R. (2014). Diabetic foot ulcer: an evidence-based treatment update. *Am J Clin Dermatol*, 15, 267–281. DOI: 10.1007/s40257-014-0081-9.

## APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
<b>ICD-10 Diagnosis Codes</b>	
E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E10.621	Type I diabetes mellitus with foot ulcer
E11.621	Type II diabetes mellitus with foot ulcer
E13.621	Other diabetes mellitus with foot ulcer
L97-L97.9	Non-pressure chronic ulcer of lower limb
L89-L89.0	Pressure ulcer
L98.4	Non-pressure chronic ulcer of skin
<b>CPT Codes</b>	
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Each additional 25 sq cm wound surface, or part thereof
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Each additional 25 sq cm wound surface, or part thereof
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Each additional 100 sq cm wound surface area or part thereof, or each additional 1% of body area of infants and children or part thereof
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound area, or 1% of body area of infants and children
15278	Each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children or part thereof
<b>HCPCS Level II Codes</b>	
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list

C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of bod
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or
Q4100	Skin substitute, NOS
Q4101	Apligraf
Q4102	OASIS wound matrix
Q4103	OASIS burn matric
Q4104	Integra BMWD
Q4105	Integra DRT
Q4106	Dermagraft
Q4107	Graftjacket
Q4108	Integra Matrix
Q4110	Primatrix
Q4111	Gammagraft
Q4112	Cymetra injectable
Q4113	Graftjacket Xpress
Q4114	Integra Flowable Wound Matrix
Q4115	Alloskin
Q4116	Alloderm
Q4117	Hyalomatrix
Q4118	Matristem Micromatrix
Q4119	Matristem Wound Matrix
Q4120	Matristem Burn Matrix
Q4121	Theraskin
Q4122	Dermacell
Q4123	Alloskin
Q4124	Oaskis Tri-layer Wound Matrix
Q4125	Arthroflex
Q4126	Memoderm/derma/tranz/integup
Q4127	Taylmed
Q4128	Flexhd/Alopatchhd/matrixhd
Q4129	Unite Biomatrix
Q4131	Epifix
Q4132	Grafix core
Q4133	Grafix prime
Q4134	HMatrix
Q4135	Mediskin
Q4136	EZderm
Q4137	Amnioexcel or Biodmatrix, 1cc
Q4138	DioDfence DryFlex, 1cc
Q4139	Amniomatrix or Biodmatrix, 1cc
Q4140	Biodfence 1cm
Q4141	Alloskin ac, 1 cm
Q4142	Xcm biologic tiss matrix 1cm
Q4143	Repriza, 1cm
Q4145	Epifix, 1mg

Q4146	Tensix, 1 cm
Q4147	Architect ecm px fx 1 sq cm
Q4148	Neox 1k, 1cm
Q4149	Excellagen, 0.1cc
Q4150	Allowrap DS or Dry 1 sq cm
Q4151	AmnioBand, Guardian 1 sq cm
Q4152	Dermapure 1 square cm
Q4153	Dermavest 1 square cm
Q4154	Biovance 1 square cm
Q4155	NeoxFlow or ClarixFlo 1mg
Q4156	Neox 100 1 square cm
Q4157	Revitalon 1 square cm
Q4158	Marigen 1 square cm
Q4159	Affinity 1 square cm
Q4160	NuSheild 1 square cm
Q9349	Fortaderm, fortaderm antimic
Q9358	SergiMend, fetal
C9360	SurgiMend, neonatal
C9363	Integra Meshed Bil Wound Mat

ICD-10-PCS (Procedure Codes)						
Section	Body System	Operation	Body Part	Approach	Device	Qualifier
<b>O</b> (Medical and surgical)	<b>H</b> (skin and breast) <b>J</b> (subcutaneous tissue and fascia) <b>R</b> (mouth and throat)	<b>R</b> (replacement) <b>U</b> (supplement) <b>W</b> (revision)	All (0-X) except: Q finger nail R toe nail S hair	<b>O</b> (open) <b>3</b> (percutaneous)	<b>J</b> (synthetic substitute) <b>K</b> (nonautologous tissue substitute)	<b>Z</b> (no qualifier)
CODES	DESCRIPTION					
OHR0	Skin, Scalp					
OHR1	Skin, Face					
OHR2	Skin, Right Ear					
OHR3	Skin, Left Ear					
OHR4	Skin, Neck					
OHR5	Skin, Chest					
OHR6	Skin, Back					
OHR7	Skin, Abdomen					
OHR8	Skin, Buttock					
OHR9	Skin, Perineum					
OHRA	Skin, Genitalia					
OHRB	Skin, Right Upper Arm					
OHRC	Skin, Left Upper Arm					
OHRD	Skin, Right Lower Arm					
OHRE	Skin, Left Lower Arm					
OHRF	Skin, Right Hand					
OHRG	Skin, Left Hand					
OHRH	Skin, Right Upper Leg					
OHRJ	Skin, Left Upper Leg					

OHRK	Skin, Right Lower Leg
OHRL	Skin, Left Lower Leg
OHRM	Skin, Right Foot
OHRN	Skin, Left Foot
OHRQ	Finger Nail
OHRR	Toe Nail
OHRS	Hair
OHRT	Breast, Right
OHRU	Breast, Left
OHRV	Breast, Bilateral
OHRW	Nipple, Right
OHRX	Nipple, Left

Note: Inclusion on this list does not guarantee coverage.

## Frequency of application and cost of skin substitutes

Product	Proposed maximum covered applications	Rationale	Medicare cost information per application (National Average Fee For Service, October, 2015*)
Apligraf	5	Greater than 5 applications not studied per FDA. Early studies limited to 5 applications, and one later study found wound healing was completed within 3 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: \$771 HOPD: \$1,495 Phys. Off = \$1,518
Derma-graft	8	The FDA prescribing information contains a caution that Dermagraft has not been studied in patients receiving greater than 8 device applications. 2003 study showed that 4 applications is equivalent to 8. Cigna limits to 8 applications in 12 weeks. One Medicare LCD limits to 8 applications.	ASC: \$771 HOPD: \$1,495 Phys. Off = \$1,409
Epifix	5	One study limited to 5 applications. Cigna limits to 4 applications in 12 weeks. Two Medicare LCD limits to 5 applications.	ASC: \$771 HOPD: \$1,495 Phys. Office: \$535
Grafix	12	Weekly applications up to 84 days in the one study	ASC: \$771 HOPD: \$1,495 Phys. Off **
Graft-jacket	1	Single application used in both studies. Cigna and one Medicare LCD limits to 1 application.	ASC: \$771 HOPD: \$1,495 Phys. Office: \$1,672
Oasis Wound Matrix	12	One study of DFU showed an average of 10 sheets. One study of VLU reported an average of 8 sheets. Study showed equivalence of 8 sheets of Oasis to 3 sheets of Dermagraft. One Medicare LCD limits to 12 weeks of therapy.	ASC: \$236 HOPD: \$518 Phys. Office: \$262
Talymed	10	Study used applications every 1-3 weeks over 20 weeks. Found fewer applications ineffective.	ASC: \$771 HOPD: \$1,495 Phys. Office **
Thera-skin	5	Up to 5 applications received in the study, however, most patients only had 1. Cigna limits to 4 applications in 12 weeks. One Medicare LCD limits to 5 applications.	ASC: \$771 HOPD: \$1,495 Phys. Office: \$612

ASC=ambulatory surgery center; DFU=diabetic foot ulcers; HOPD=hospital outpatient department; LCD=local coverage determination; VLU=venous leg ulcers

\*Costs reported are for the smallest available product and include applicable professional fees for applying the skin substitute to a leg ulcer smaller than 25 cm<sup>2</sup>. Fees are higher for some other body parts or larger applications.

\*\*Physician's office average sales price (ASP) fees cannot be calculated, product not on ASP fee schedule.

**References for pricing information:**

Hospital outpatient bundle costs retrieved from

<https://www.cms.gov/apps/ama/license.asp?file=/hospitaloutpatientpps/downloads/2015-Jan-Addendum-B-File.zip>

Ambulatory surgical center bundled rates retrieved from

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2015-October-ASC-Addenda.zip>

Physician fees retrieved from

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html?redirect=/PhysicianFeeSched/>

October 2015 ASP Pricing file (for physician's office product fees) retrieved from:

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2015ASPFiles.html>

All retrievals made October 29, 2015.

# Section 3.0

## Coverage Guidances

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## DIGITAL BREAST TOMOSYNTHESIS FOR BREAST CANCER SCREENING

<b>Population description</b>	Women between the ages of 40 and 74 years referred for breast cancer screening <i>Population scoping notes: Exclude women with a personal history of breast cancer or ductal carcinoma in situ; BRCA mutations</i>
<b>Intervention(s)</b>	Digital breast tomosynthesis (3-D mammography) <del>or digital breast tomosynthesis in conjunction with standard 2-D mammography</del> <a href="#">with or without standard digital mammography</a> <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Standard 2-D mammography with or without computer-aided diagnosis, no screening, MRI for breast cancer screening
<b>Outcome(s) (up to five)</b>	Critical: Breast cancer morbidity and mortality, quality of life Important: Cancer detection rate ( <a href="#">invasive</a> ), recall rate for false positive tests including additional invasive and non-invasive testing <i>Considered but not selected for GRADE Table: All-cause mortality, radiation exposure</i>
<b>Key questions</b>	<ol style="list-style-type: none"><li>1. What is the effectiveness of digital breast tomosynthesis as a primary screening modality in women referred for breast cancer screening?</li><li>2. Does the effectiveness of digital breast tomosynthesis as a primary screening modality vary by the following characteristics:<ol style="list-style-type: none"><li>a. Age</li><li>b. Breast density</li><li>c. Baseline risk (as ascertained by risk assessment tools)</li><li>d. Screening interval</li></ol></li><li>3. In a screening population, how do the operating characteristics of digital breast tomosynthesis compare to those of standard 2-D mammography?</li></ol>
<b>Contextual questions</b>	None

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## DIGITAL BREAST TOMOSYNTHESIS FOR BREAST CANCER SCREENING

### CHANGE LOG

Date	Change	Rationale
1/26/2016	Changed interventions to Digital breast tomosynthesis (3-D mammography) with or without standard digital mammography. Reworded for brevity and clarity but chose not to limit scope at this time.	Public comment suggested removing DBT alone from interventions.

DRAFT

Date received: 1/15/2016 at 4:26 pm  
Associate Professor of Radiology  
Teaching hospital

To whom it may concern,

With respect to the "Interventions" section, it should be noted that in the US, Digital Breast Tomosynthesis is only approved to be used with both the 2D and 3D information. Accordingly, the vast majority of scientific publications compare combined 2D/3D imaging with 2D imaging alone. As a radiologist who reads digital breast tomosynthesis exams on a daily basis I want to be very clear that I, and my colleagues throughout Oregon and the United States, read BOTH the 2D image set and the 3D image set side-by-side on patients. Our workstations acquire the 2D image sets to be used for comparing priors (2D compared to 2D) as well as the 3D image sets to scan through each slice of the breast on that same patient to find cancer the 2D mammography alone misses, or rule out suspicious lesions, masses and calcifications so the patient does not need to be recalled unnecessarily as a false-positive for additional testing.

I am attaching a PDF of publications released only during 2015, but please be aware the body of evidence going as far back as 2011 supports my comments above on a consistent basis with regard to study design comparing 2D/3D to 2D imaging alone (over 100 studies). At a later date I would like the opportunity to share the most significant of those with the HERC.

Date received: 1/16/2016 at 11:39 am  
Radiologist, specializing in women's imaging  
Radiology clinic

Regarding the Outcomes section of the scope statement, I strongly disagree that “morbidity and mortality, quality of life” are “critical outcomes” when evaluating an improved mammography technique such as DBT. The link between the early detection of invasive cancer with mammography and reduced breast cancer mortality is already very well established. Thus, when evaluating the potential benefits of a new mammography technology, it is sufficient to evaluate the ability of this new technology to detect invasive cancers. A long term study evaluating breast cancer mortality rates with DBT is not necessary to understand the potential benefits compared to traditional mammography. Furthermore, with a large body of published data showing that DBT finds more cancers than traditional mammography, it is unlikely a randomized controlled trial comparing the mortality rates of DBT and traditional mammography will ever be conducted because it would be impractical and potentially unethical to randomly assign women to receive a lifetime of screening with traditional mammography.

The National Institute of Health articulates this position very clearly in its publication “Fundamental Concepts for Health Technology Assessments”:

***“Beyond technical performance of screening and diagnostic tests, their effect on health outcomes or health-related quality of life is often less immediate or direct than for other types of technologies. The impacts of most preventive, therapeutic, and rehabilitative technologies on health outcomes can be assessed as direct cause-and-effect relationships between interventions and outcomes. However, the relationship between the use of screening and diagnostic tests and health outcomes is typically indirect, given intervening decisions or other steps between the test and health outcomes. Even highly accurate test results may be ignored or improperly interpreted by clinicians. Therapeutic decisions that are based on test results can have differential effects on patient outcomes. Also, the impact of those therapeutic decisions may be subject to other factors, such as patient adherence to a drug regimen.”***

It is well documented in studies with over 50,000 patients that standard 2D mammography finds cancer. It is even better documented in studies with over 200,000 patients that DBT finds more cancer. Even if DBT found the same numbers of cancer as standard 2D mammography, there is not a need to evaluate “morbidity and mortality, quality of life”, because this has already been proven out. If this were not so, then standard 2D mammography would not be available to your members or inclusive as a preventive service under USPSTF. The proposed Critical outcomes are unreasonable and unnecessary endpoints, and not a worthwhile investment of the HERC’s time. It is my opinion these should be removed from the Scope Statement.

As an alternative I would like to suggest that the most critical outcomes are cancer detection rate, invasive cancer detection rate, recall rate, PPV for recalls and PPV for biopsies. These outcomes are listed as Important, but should instead be listed as Critical because it is these outcomes that drive morbidity, mortality and quality of life. It is these five endpoints that will ultimately determine (and improve) morbidity, mortality and quality of life. Therefore, these five should be the Critical outcomes the HERC spends its time focused on and assessing.

## SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

### Fecal Microbiota Transplantation for Clostridium difficile Infection

<b>Population description</b>	Adults and children with Clostridium difficile infection (CDI) <i>Population scoping notes: None</i>
<b>Intervention(s)</b>	Fecal microbiota transplantation (FMT) by any route <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Oral or intravenous metronidazole, oral or rectal vancomycin, oral rifaximin, oral fidaxomicin, bile acid sequestrants, combinations of these treatments, probiotics
<b>Outcome(s) (up to five)</b>	Critical: Mortality, CDI-related morbidity (including hospitalizations), symptom resolution without recurrence  Important: Iatrogenic infections, harms from intervention (e.g., colon perforation, antibiotic side effects)  <i>Considered but not selected for GRADE Table: None</i>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of FMT for patients with CDI?</li> <li>2. Does the effectiveness, harm, or patient acceptance of FMT for CDI vary by:             <ol style="list-style-type: none"> <li>a. Initial vs recurrent vs refractory infection</li> <li>b. Previous treatment regimen</li> <li>c. Severity of infection</li> <li>d. Route of administration</li> <li>e. Donor characteristics</li> </ol> </li> </ol>
<b>Contextual questions</b>	None

#### CHANGE LOG

Date	Change	Rationale
m/d/yyyy		

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## GENETIC TESTING TO GUIDE USE OF ANTI-DEPRESSANT MEDICATIONS

<b>Population description</b>	<p>Adults or children with major depressive disorder who are initiating or changing anti-depressant medications</p> <p><i>Population scoping notes: None</i></p>
<b>Intervention(s)</b>	<p>Genetic testing to inform the selection of anti-depressant medications</p> <p><i>Intervention exclusions: None</i></p>
<b>Comparator(s)</b>	<p>Usual care</p>
<b>Outcome(s) (up to five)</b>	<p>Critical: Depression remission, functional improvement, quality of life</p> <p>Important: Timing to remission, depression improvement</p> <p><i>Considered but not selected for GRADE Table: Total health care costs</i></p>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. Are genetic tests to guide selection of anti-depressant medications analytically valid?</li> <li>2. Are genetic tests to guide selection of anti-depressant medications clinically valid?             <ol style="list-style-type: none"> <li>a. Do these tests predict the likelihood of responding to anti-depressant medications?</li> <li>b. Do these tests predict the likelihood of discontinuation of anti-depressant medications?</li> </ol> </li> <li>3. Are genetic tests to guide selection of anti-depressant medications clinically useful?             <ol style="list-style-type: none"> <li>a. Do these tests change the treatments selected by physicians and patients?</li> </ol> </li> <li>4. Do these tests improve depression or quality of life outcomes for patients?</li> <li>5. Does the clinical utility of these tests vary by:             <ol style="list-style-type: none"> <li>a. Whether the depression is an initial or recurrent episode</li> <li>b. Chronicity</li> <li>c. Severity of depression</li> </ol> </li> <li>6. <a href="#"><u>Does the use of genetic testing to guide use of anti-depressant medication reduce total health care costs?</u></a></li> </ol>

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## GENETIC TESTING TO GUIDE USE OF ANTI-DEPRESSANT MEDICATIONS

### CHANGE LOG

Date	Change	Rationale
1/26/2016	Added Key Question 6 on impact on total health care costs.	In response to public comment.

DRAFT

Comments received: 1/22/2016  
From: National Account Manager Government Accounts  
Organization: Pharmacogenetics laboratory

## **Comments pertaining to the Scope Statement for HERC Coverage Guidance**

### **“Genetic Testing to Guide Use of Anti-Depressant Medications”**

#### **Population Description:**

The GeneSight test is intended to aid in the selection of anti-depressant medications for patients with major depressive disorder who have failed at least one medication and a change in medication is being considered. We are not intended for a treatment naive patient population.

#### **Intervention:**

Intervention is appropriate

#### **Comparator:**

Treatment as Usual

#### **Outcomes**

Critical: Depression response (defined as a 50% decrease in baseline HAMD-17 score), Depression remission (defined as HAMD-17 score of < 7), quality of life

Important: Timing to response, timing to remission, depression improvement, reduction in polypharmacy

If we can add a question, I would suggest:

Are genetic tests able to reduce total health care costs?

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## INTERVENTIONS TO REDUCE THE HARMS OF TOBACCO DURING PREGNANCY

<b>Population description</b>	Women during pregnancy and the postpartum period <i>Population scoping notes: Includes all forms of tobacco, including e-cigarettes</i>
<b>Intervention(s)</b>	Screening for tobacco use, pharmacotherapy, behavioral interventions (telephonic, in person, individual, group), Internet based interventions, and multisector interventions such as policy, systems, and environmental change <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	No care, usual care, other studied interventions
<b>Outcome(s) (up to five)</b>	Critical: Pregnancy complications, low birth weight, perinatal/infant death Important: Abstinence from tobacco during pregnancy, long-term tobacco abstinence <i>Considered but not selected for GRADE Table: Maternal exposure to secondhand smoke, health benefits to mothers.</i>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What interventions are most effective and most cost-effective to:             <ol style="list-style-type: none"> <li>a. Reduce tobacco-related perinatal/infant morbidity and mortality?</li> <li>b. Reduce tobacco use prevalence in pregnant women?</li> <li>c. Sustain tobacco abstinence after delivery among women who quit tobacco use during pregnancy?</li> </ol> </li> <li>2. Does effectiveness vary by socioeconomic factors such as race, ethnicity, income and educational attainment?</li> <li>3. What models of care would allow these interventions to be implemented most effectively and cost-effectively?</li> </ol>

### CHANGE LOG

Date	Change	Rationale
m/d/yyyy		

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## GASTROINTESTINAL MOTILITY TESTS

<b>Population description</b>	<p>Adults and children with suspected gastrointestinal motility disorders (e.g., gastroparesis, colonic pseudo-obstruction, slow-transit constipation)</p> <p><i>Population scoping notes: None</i></p>
<b>Intervention(s)</b>	<p>Radiographic and capsule-based gastrointestinal motility tests:</p> <ul style="list-style-type: none"> <li>• Gastric emptying scintigraphy</li> <li>• Radiopaque marker testing</li> <li>• Barium small bowel follow through</li> <li>• Colonic scintigraphy</li> <li>• Whole gut scintigraphy</li> <li>• Wireless motility capsule</li> <li>• Isotope breath tests</li> </ul> <p><i>Intervention exclusions: None</i></p>
<b>Comparator(s)</b>	<p>No testing, other listed interventions, <a href="#">usual care (diagnosis based on clinical criteria/assessment tools)</a> <del>diagnosis based on clinical criteria/assessment tools,</del> <del>empiric therapy</del></p>
<b>Outcome(s) (up to five)</b>	<p>Critical: Patient-reported symptoms, quality of life, morbidity (including hospitalization)</p> <p>Important: Change in management, harms of intervention</p> <p><i>Considered but not selected for GRADE Table: Need for additional testing, diagnostic accuracy (will be reported as contextual information), need for further testing</i></p>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of gastrointestinal motility tests for patients with suspected motility disorders?</li> <li>2. What is the diagnostic accuracy of gastrointestinal motility tests in patients with suspected motility disorders?</li> <li>3. What are the harms of gastrointestinal motility tests for patients with suspected motility disorders?</li> </ol>
<b>Contextual questions</b>	<p><a href="#">1. What is the diagnostic accuracy of the interventions?</a></p>

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## GASTROINTESTINAL MOTILITY TESTS

### CHANGE LOG

Date	Change	Rationale
1/28/2016	Added diagnostic accuracy as a contextual question	Based on decision above not to include this as an outcome.

DRAFT

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## TIMING OF LONG-ACTING REVERSIBLE CONTRACEPTIVE PLACEMENT

<b>Population description</b>	Women in the post-partum or post-abortal period who desire contraception <i>Population scoping notes: None</i>
<b>Intervention(s)</b>	Offering immediate post-partum or post-abortal placement of a long-acting reversible contraceptive (LARC) <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Usual care: offering immediate non-LARC forms of contraception, scheduling delayed LARC placement, delaying discussion of options until 6 weeks post-partum or post-abortion
<b>Outcome(s) (up to five)</b>	Critical: Pregnancies, abortions Important: Presence of LARC at one year, need for alternate/replacement contraception, procedural harms <i>Considered but not selected for GRADE Table: Patient satisfaction, device expulsion, discontinuation of contraception for any reason other than desire to conceive</i>
<b>Key questions</b>	<ol style="list-style-type: none"><li>1. What is the comparative effectiveness of offering immediate post-partum or post-abortal placement of a long-acting reversible contraceptive?</li><li>2. What are the harms of immediate post-partum or post-abortal placement of a long-acting reversible contraceptive?</li></ol>

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## PERCUTANEOUS INTERVENTIONS FOR LOW BACK PAIN

<b>Population description</b>	Adults with acute, <a href="#">subacute</a> , or chronic low back pain <a href="#">with or without radiculopathy</a> <i>Population scoping notes: None</i>
<b>Intervention(s)</b>	Epidural, facet joint, or sacroiliac corticosteroid injections <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Other injection therapies (e.g., local anesthetics, hyaluronic acid, or saline), physical therapy, home exercise programs, medications (e.g., oral corticosteroids, opioids, nonsteroidal anti-inflammatory drugs), complementary and alternative therapies (e.g., acupuncture, yoga, chiropractic therapy), soft tissue injections, ablative interventions, no treatment, <a href="#">surgery</a>
<b>Outcome(s) (up to five)</b>	Critical: Short-term function, long-term function, long-term risk of undergoing surgery  Important: Adverse events, change in utilization of comparators  <i>Considered but not selected for GRADE Table: Immediate-, short- and long-term pain, immediate-term function.</i>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of corticosteroid injection therapies for low back pain?</li> <li>2. Does the effectiveness of corticosteroid injection therapies for low back pain vary based on:             <ol style="list-style-type: none"> <li>a. <a href="#">Duration of back pain</a> <del>Acute vs chronic back pain</del></li> <li>b. Etiology of back <a href="#">or radicular</a> pain (e.g., stenosis, <del>radicular pain</del>, <a href="#">disc herniation</a>)</li> <li>c. Choice of corticosteroid, dose, or frequency</li> <li>d. Anatomic approach</li> <li>e. Use of imaging guidance</li> <li>f. Previous back surgery</li> <li>g. <a href="#">Response to previous diagnostic injections</a></li> <li>h. <a href="#">Response to previous injection therapies</a></li> </ol> </li> <li>3. What are the harms of corticosteroid injection therapies for low back pain?</li> </ol>

# SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

## PERCUTANEOUS INTERVENTIONS FOR LOW BACK PAIN

<b>Contextual questions</b>	<ol style="list-style-type: none"><li>1. Does the use of these therapies influence subsequent utilization of health care resources (e.g., chiropractic, opioids, acupuncture, physical therapy)?</li><li>2. Does the effectiveness of these interventions depend on prior treatments the patient has received?</li></ol>
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### CHANGE LOG

Date	Change	Rationale
1/26/2015	<ol style="list-style-type: none"><li>1. Added subacute to population, and qualified that pain could be with or without radiculopathy</li><li>2. Added surgery to comparators</li><li>3. Changed Key Question 2:<ol style="list-style-type: none"><li>a. duration of back pain rather than whether the pain was acute or chronic</li><li>b. Changed "Etiology of back pain (e.g. stenosis, radicular pain)" to "Etiology of back or radicular pain (e.g. stenosis, disc herniation)"</li><li>c. Added "response to previous diagnostic injections"</li></ol></li></ol>	Based on public comment

Received: 1/11/2016 at 3:31 pm

From: Physician Assistant and Certified Teacher of the Alexander Technique  
Portland Oregon

Comment:

The gold standard here is the evidence supporting long term benefit in those with chronic back pain. Studies should show benefit at one year in those with pain that has been persist for over 6 months.

There are only two interventions that have this type of evidence and injections is not one of them.

Further, we should prefer therapies that that have shown savings. Arguably, given the terrible problem of narcotic diversion, studies showing that this intervention also decreases medication needs is the most important. Finally safety should be a concern, and of course injections have well known risks.

The only intervention that meets all the above requirements is the Alexander Technique. I can refer you to studies that support this.

I oppose supporting interventions that do not have this levels of evidence when better alternatives are available.

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Received: 1/19/2016  
President  
Specialty Society

The Spine Intervention Society, a multi---specialty association of 3,000 physicians dedicated to the development and promotion of high quality interventional spine care, extends to Oregon Health Authority (OHA) an offer to provide expert input. We are fully cognizant of inappropriate utilization, and therefore wish to identify effective interventions. Without appropriate questions and evidence inclusion/exclusion criteria the report will not facilitate such determinations, leading to egregious denial of access to procedures for many patients. The methodology and questions must be revised to ensure that the **highest quality evidence** is addressed scientifically, providing an accurate assessment of these procedures.

The current Coverage Guidance indicates that the topic will be reviewed following publication of the AHRQ technology assessment on spinal injections for low back pain (LBP). (1) Unfortunately, that report is of limited utility, suffering from significant methodological flaws. (2) Therefore, it is critical that OHA be aware of these errors and not repeat them.

### **PICO**

#### **Methodology**

- Population Description: Add sub---acute LBP. If the review is intended to address radicular pain, this should be included here and in the title. It is a separate entity from LBP.
- Interventions: For ablative procedures, develop questions appropriately assessing their effectiveness.
- Comparators: Include surgery.
- Outcomes: Short---term pain relief, short---term functional improvement, and impact on utilization of opioids are critical outcomes to consider in the GRADE assessment.

### **Questions**

Key question #1 is unnecessary. It is covered better by Question #2.

Key question #2:

- It is critical to assess the effectiveness of each procedure for each diagnosis/etiology (with imaging---confirmed pathology), with subgroup analysis by use of image guidance and different approach/access technique. (2)
- Like back pain, radicular pain is a symptom. Suggest for b: “etiology of back

**or**

radicular pain (e.g. stenosis, disc herniation)". Since evidence differs for treatment of back versus radicular pain, sub---questions should treat the two separately.

- If assessing ablative interventions, it is important to include: "g. response to previous diagnostic injections" and "h. response to previous injection therapies".

Studies have demonstrated that up to 74% of "epidural" steroid injections performed without image guidance either deposit medication external to the epidural space or do not reach the targeted pathology within the ventral epidural space. (3---6). It is critical that studies included in the review are restricted to those that use image guidance to ensure that medications have been delivered to the target.

There are very few RCTs that utilized current practice standards. Hence examination of current large observational studies adds critical information relevant to current standards of practice. (7---10) Recent methodology literature suggests that effect estimates from high quality observational trials do not differ significantly from RCTs. (9) Categorical data must be used wherever available and weighted more heavily than continuous data. (2,11)

Key question #3 must stratify by type of procedure, diagnosis, use of image guidance, injectate (particulate or non---particulate steroid), and technical accuracy. Serious irreversible complications are exceedingly rare and have yet to be reported in most spinal injections performed in accordance with guidelines. (10,12,13)

### References:

1. Chou R, Hashimoto R, Friedly J, Fu Rochelle, Dana T, Sullivan S, Bougatsos C, Jarvik J. Pain management injection therapies for low back pain. Technology Assessment Report ESIB0813. (Prepared by the Pacific Northwest Evidence---based Practice Center under Contract No. HHS 290---2012---00014---I.) Rockville, MD: Agency for Healthcare Research and Quality; March 2015.
2. Multisociety Letter to the Agency for Healthcare Research and Quality: Serious Methodological Flaws Plague Technology Assessment on Pain Management Injection Therapies for Low Back Pain. Pain Med 2015.
3. Fredman B, Nun MB, Zohar E, Iraqi G, Shapiro M, Gepstein R, Jedeikin R. Epidural steroids for treating "failed back surgery syndrome": is fluoroscopy really necessary? Anesth Analg 1999; 88 (2): 367---72.
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- Med Rehabil 2008; 89 (3): 413---6.
7. Sackett DL, Rosenberg WM, Gray JA., Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312,71-72.
  8. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *NEJM* 2000;342:1887-1892.
  9. Anglemeyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev.* 2014 Apr 29;4:MR000034.
  10. Bogduk N (ed). *Practice Guidelines for Spinal Diagnostic and Treatment Procedures*, 2<sup>nd</sup> edn. International Spine Intervention Society, San Francisco, 2013.
  11. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino J, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Korff MV, Weiner DK. Report of the NIH Task Force on research standards for chronic low back pain. *Pain Med* 2014; 15 (8):1249---67.
  12. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, Riew KD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fourney DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 2015; 122 (5): 974---84.
  13. El---Yahchouchi CA, Plastaras CT, Maus TP, Carr CM, McCormick ZL, Geske JR, Smuck M, Pingree MJ, Kennedy DJ. Adverse event rates associated with transforaminal and interlaminar epidural steroid injections: A multi---institutional study. *Pain Med.* 2015 Nov 23.

### **Additional Peer Reviewed Literature Attached for Consideration in the Review:**

1. Dreyfuss P, Halbrook B, Pauza K, Joshi A, McLarty J, Bogduk N. Efficacy and validity of radiofrequency neurotomy for chronic lumbar zygapophysial joint pain. *Spine (Phila Pa 1976)*. 2000 May 15;25(10):1270---7.
2. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010;11:1149–68.
3. Ghai B, Bansal D, Kay JP, Vadaje KS, Wig J. Transforaminal versus parasagittal interlaminar epidural steroid injection in low back pain with radicular pain: a randomized, double---blind, active---control trial. *Pain Physician*. 2014 Jul---Aug;17(4):277---90.
4. Kaufmann, T. J. et al. Clinical effectiveness of single lumbar transforaminal epidural steroid injections. *Pain Med* 2013;14:1126–1133.
5. Ghai B, Kumar K, Bansal D, Dhatt SS, Kanukula R, Batra YK. Effectiveness of parasagittal interlaminar epidural local anesthetic with or without steroid in chronic lumbosacral pain: a randomized, double---blind clinical trial. *Pain Physician*. 2015 May---Jun;18(3):237---48.
6. Kennedy, D. J. et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double---blind trial. *Pain Med* 2014;15:548–555.
7. Kennedy DJ, Engel A, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J. Fluoroscopically Guided Diagnostic and Therapeutic Intra---Articular Sacroiliac Joint Injections: A Systematic Review. *Pain Med*. 2015 Aug;16(8):1500---18.
8. Kennedy DJ, Levin J, Rosenquist R, Singh V, Smith C, Stojanovic MP, Vorobeychik Y. Epidural steroid injections are safe and effective: Multisociety letter in support of the safety and effectiveness of epidural steroid injections. *Pain Med*. 2015 May;16(5):833---8.
9. King W, Ahmed SU, Baisden J, Patel N, Kennedy DJ, MacVicar J, Duszynski B. Diagnosis and treatment of posterior sacroiliac complex pain: a systematic review with comprehensive analysis of the published data. *Pain Med*. 2015 Feb;16(2):257--65.
10. MacVicar J, Borowczyk JM, MacVicar AM, Loughnan BM, Bogduk N. Lumbar medial branch radiofrequency neurotomy in New Zealand. *Pain Med*. 2013 May;14(5):639---45.
11. MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: A comprehensive review with systematic analysis of the published data. *Pain Med* 2013;14:14–28.
12. Multisociety Letter to the Agency for Healthcare Research and Quality: Serious Methodological Flaws Plague Technology Assessment on Pain Management Injection Therapies for Low Back Pain. *Pain Med* 2015.
13. Riew KD, Yin Y, Gilula L, et al. The effect of nerve root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double---blind study. *J Bone Joint Surg Am* 2000;82:1589–93.

Received: 1/19/2016 at 8:55 am  
From: Senior Director of Policy and Practice  
Specialty Society

Good morning,

On behalf of Dr. John MacVicar, President of the Spine Intervention Society, attached please find comments on the draft scope statement for the coverage guidance on percutaneous interventions for low back pain. The Spine Intervention Society, a multi-specialty association of 3,000 physicians dedicated to the development and promotion of high quality interventional spine care, extends to Oregon Health Authority an offer to provide expert input. We are fully cognizant of inappropriate utilization, and therefore wish to bring into focus which interventions are effective. Without appropriate questions and evidence inclusion/exclusion criteria, the report will not assist in making such determinations, and the conclusions may lead to egregious denial of access to procedures for many patients suffering from low back and/or radicular pain. We trust that the PICO methodology and questions will be revised to ensure the **highest quality evidence** is addressed scientifically to provide an accurate assessment of these procedures.

In the future, we urge Oregon Health Authority to provide a **longer comment period in order to ensure submission of thoughtful and comprehensive feedback**. Additionally, the **500 word restriction has precluded submission of additional suggestions that we believe would be quite useful in formulating key questions and the methodology** that will guide a thorough and appropriate review of these procedures. Additionally, there are a great many studies that would be important to review, but the short turnaround time precluded compilation of a comprehensive reference list.

Again, we encourage you to contact us as we can assist with providing appropriate national and international experts to provide input as you outline the important questions and applicable evidence to answer them. We would greatly appreciate a confirmation of receipt of our attached comments.

Best wishes,

# Management of Recurrent Acute Otitis Media in Children – 2015 Rescanning Summary

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**Subcommittee:** Evidence-based Guidelines Subcommittee (HERC approved August 2013)

**EbGS Recommendation:** Develop a new coverage guidance to update this topic.

**Bottom Line:** The evidence for adenoidectomy and/or tympanostomy tubes for recurrent acute otitis media (AOM) is mixed with several new publications since the initial coverage guidance was issued. There appears to be no new summary evidence on the effectiveness of prophylactic antibiotics for recurrent AOM, though it should be noted that AAP guidelines recommend against it.

## Coverage Recommendation (Box Language)

Prophylactic antibiotics should be covered for recurrent acute otitis media.\*

Tympanostomy tubes may be covered for acute otitis media only for recurrent acute otitis media.

Adenoidectomy or adenotonsillectomy should not be covered for the treatment of recurrent acute otitis media.

*\*Recurrent acute otitis media is defined here as three or more episodes in six months or four or more episodes in one year.*

*Note: Coverage guidance for chronic otitis media with effusion is addressed in a separate document.*

## Scope Statement

<b>Population description</b>	Children with recurrent acute otitis media (AOM) <i>Population scoping notes: None</i>
<b>Intervention(s)</b>	Prophylactic or suppressive antibiotics, tympanostomy tubes (grommets), tonsillectomy and/or adenoidectomy (note that these interventions may be used alone, serially or in combination) <i>Intervention exclusions: None</i>
<b>Comparator(s)</b>	Usual care, episodic treatment of AOM

<b>Outcome(s) (up to five)</b>	<p><i>Critical:</i> Severe infection (e.g., systemic infection, sepsis, meningitis, locally invasive infection), clinically significant hearing loss, speech delay</p> <p><i>Important:</i> Treatment harms, acute otitis media episodes</p> <p><i>Outcomes considered but not selected for GRADE table:</i> Missed school days, school performance/academic achievement</p>
<b>Key questions</b>	<ol style="list-style-type: none"> <li>1. What is the comparative effectiveness of interventions (alone, serially, or in combination) for recurrent acute otitis media? <ol style="list-style-type: none"> <li>a. Are there subpopulations of children with recurrent acute otitis media who are more likely to benefit from prophylactic interventions?</li> </ol> </li> <li>2. What are the harms of interventions for recurrent acute otitis media?</li> </ol>

### Original Evidence Sources

- Leach, A. J., & Morris, P.S. (2006). Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews*, 4(CD004401), 1-70. [Assessed as up-to-date: 5 AUG 2010]. Retrieved from <http://summaries.cochrane.org/CD004401/antibiotics-to-prevent-acute-earinfections-in-children>
- McDonald, S., Langton Hewer, C. D., & Nunez, D. A. (2008). Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database of Systematic Reviews*, 4(CD 004741), 1-14. [Assessed as up-to-date: 10 JAN 2011]. Retrieved from <http://summaries.cochrane.org/CD004741/grommets-ventilation-tubes-for-recurrentacute-otitis-media-in-children>
- Shekelle, P. G., Takata, G., Newberry, S.J., Coker, T., Limbos, M., Chan, L. S., ... Shanman, R. (2010). *Management of Acute Otitis Media: Update*. Evidence Report/Technology Assessment No. 198. (Prepared by the RAND Evidence-Based Practice Center under Contract No. 290 2007 10056 I). Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK56132/>

## Scanning Results

1. Boonacker, C. W., Rovers, M. M., Browning, G. G., Hoes, A. W., Schilder, A. G., & Burton, M. J. (2014). Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technology Assessment, 18*(5), 1-117.

Citation 1 is a health technology assessment by the NHS and includes a meta-analysis of 10 trials of adenoidectomy with or without grommets. In the meta-analysis, adenoidectomy with or without grommets had a failure rate (defined as >4 episodes of AOM over 12 months) of 32% compared with 45% in the group that did not undergo adenoidectomy. The benefit of adenoidectomy for recurrent AOM appeared to be greatest in children under the age of 2 years.

2. Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Tympanostomy tube insertion system for children with otitis media*. Ottawa: CADTH. Retrieved from [https://www.cadth.ca/sites/default/files/pdf/EH0018\\_TympanostomyTubeInsertionDelivery\\_e.pdf](https://www.cadth.ca/sites/default/files/pdf/EH0018_TympanostomyTubeInsertionDelivery_e.pdf)

Citation 2 is a CADTH brief summary on the TULA system for placing tympanostomy tubes in the outpatient setting using local anesthesia only. Based on three single-arm, open-label, prospective trials the TULA system appears to be safe and cost-effective. It should be noted that there are competing technologies under development.

3. Cheong, K. H., & Hussain, S. S. (2012). Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. *Journal of Laryngology & Otology, 126*(9), 874-85.

Citation 3 is a systematic review that includes seven studies examining various interventions for recurrent AOM. The authors conclude that prophylactic antibiotics and adenoidectomy both reduce recurrence of AOM, but tympanostomy tubes do not.

4. Courter, J. D., Baker, W. L., Nowak, K. S., Smogowicz, L. A., Desjardins, L. L., Coleman, C. I., & Giroto, J. E. (2010). Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Annals of Pharmacotherapy, 44*(3), 471-478.

Citation 4 is a meta-analysis of studies comparing macrolides to beta-lactam antibiotics for AOM. It is out of scope.

5. Gaboury, I., Coyle, K., Coyle, D., & Le Saux, N. (2010). Treatment cost effectiveness in acute otitis media: a watch-and-wait approach versus amoxicillin. *Paediatrics and Child Health*, 15(7), e14-e18.

Citation 5 is a Canadian cost-effectiveness study comparing watchful-waiting to amoxicillin treatment for AOM. It is out of scope.

6. Gisselsson-Solen, M. (2014). The importance of being specific – a meta-analysis evaluating the effect of antibiotics in acute otitis media. *International Journal of Pediatric Otorhinolaryngology*, 78(8), 1221-1227.

Citation 6 is meta-analysis that addresses methodologic issues in the selection of outcomes for trials of antibiotic treatment of AOM. It is out of scope.

7. Hellstrom, S., Groth, A., Jorgensen, F., Pettersson, A., Ryding, M., Uhlen, I., & Bostrom, K. B. (2011). Ventilation tube treatment: a systematic review of the literature. *Otolaryngology – Health & Neck Surgery*, 145(3), 383-95.

Citation 7 is a systematic review of 63 studies of “secretory otitis media.” The authors conclude that tympanostomy tubes are associated with improve QoL but there is insufficient evidence of an effect on recurrent AOM.

8. Kozyrskyj, A. L., Klassen, T. P., Moffatt, M., & Harvey, K. (2010). Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 9. DOI: 10.1002/14651858.CD001095.pub2.

Citation 8 is a Cochrane review of short-course antibiotic treatment of AOM. It is out of scope.

9. Lieberthal, A. S., Carroll, A. E., Chonmaitree, T., Ganiats, T. G., Hoberman, A., Jackson, M. A., ... Tunkel, D. E. (2013). The diagnosis and management of acute otitis media. *Pediatrics*, 131(3), e964-99.

Citation 9 is a CPG from the American Academy of Pediatrics. The guidelines state that prophylactic antibiotics should not be prescribed for the treatment of recurrent AOM (evidence level: B, strength: recommendation). Tympanostomy tubes can be offered for recurrent AOM (evidence level: B, strength: option).

10. Lous, J., Ryborg, C. T., & Thomsen, J. L. (2011). A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *International Journal of Pediatric Otorhinolaryngology*, 75(9), 1058-61.

Citation 10 is a systematic review of tympanostomy tubes for recurrent AOM. The authors conclude that 2 to 5 children need to receive tympanostomy tubes in order to prevent one episode of recurrent AOM over 6 months. The authors note that this appears to be similar to the effects of six months of prophylactic antibiotic treatment.

11. Mikals, S. J., & Brigger, M. T. (2014). Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. *JAMA Otolaryngology - Head and Neck Surgery*, 140(2), 95-101.

Citation 11 is a SR and MA of 15 trials of adenoidectomy in addition to tympanostomy tube placement for treatment of recurrent AOM, otitis media with effusion, or otorrhea. The study results were mixed and heterogeneous, but in the meta-analysis addition of adenoidectomy reduced the need for repeated tympanostomy tubes, although the effects appeared to be attenuated in children under the age of 4 years.

12. Rosenfeld, R. M., Schwartz, S. R., Pynnonen, M. A., Tunkel, D. E., Hussey, H. M., Fichera, J. S., ... Schellhase, K. G. (2013). Clinical practice guideline: tympanostomy tubes in children. *Otolaryngology - Head and Neck Surgery*, 149(1 Suppl):S1-35.

Citation 12 is a CPG from the American Academy of Otolaryngology – Head and Neck Surgery. The guidelines recommend that tympanostomy tubes should not be offered for treatment of recurrent AOM unless a middle ear effusion is present at the time of evaluation for tubes.

13. Subcommittee of Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children (Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology). (2012). Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. *Auris, Nasus, Larynx*, 39(1), 1-8.

Citation 13 is multi-society CPG from several ENT societies in Japan pertaining to treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

14. Thanaviratnanich, S., Laopaiboon, M., & Vatanasapt, P. (2013). Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 12. DOI: 10.1002/14651858.CD004975.pub3.

Citation 14 is a Cochrane review comparing the effectiveness of various dosing regimens for the treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

15. Thorton, K., Parrish, F., & Swords, C. (2011). Topical vs. systematic treatments for acute otitis media. *Pediatric Nursing*, 37(5), 263-7.

Citation 15 is a narrative review of treatment strategies for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

16. Toll, E. C., & Nunez, D. A. (2012). Diagnosis and treatment of acute otitis media: review. *Journal of Laryngology & Otology*, 126(10), 976-83.

Citation 16 is a narrative review of the diagnosis and treatment of AOM. It does not specifically address the treatment of recurrent AOM except to briefly note that tympanostomy tubes reduce recurrent AOM.

17. van den Aardweg, M. T. A., Schilder, A. G. M., Herkert, E., Boonacker, C. W. B., & Rovers, M. M. (2010). Adenoidectomy for otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 1. Art. DOI: 10.1002/14651858.CD007810.pub2.

Citation 17 is a Cochrane review of adenoidectomy compared with tympanostomy tubes or non-surgical management in children with otitis media with effusion. The authors conclude that the studies of adenoidectomy did not demonstrate a significant benefit in reducing episodes of AOM.

18. Venekamp, R. P., Sanders, S. L., Glasziou, P. P., Del Mar, C. B., & Rovers, M. M. (2015). Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 6. DOI: 10.1002/14651858.CD000219.pub4.

Citation 18 is a Cochrane review of antibiotic treatment for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

19. Venekamp, R. P., Damoiseaux, R. A. M. J. & Schilder, A. G. M. (2014). Acute otitis media in children. *BMJ Clinical Evidence*, 09, 301-322.

Citation 19 is a BMJ Clinical Evidence brief on the diagnosis and management of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

20. Washington Health Technology Assessment (WA HTA). (2015). *Tympanostomy tubes in children – draft evidence report*. Olympia, WA: WA HTA. Retrieved August 12, 2015 from [http://www.hca.wa.gov/hta/Documents/tympan\\_tubes\\_draft\\_report\\_073115.pdf](http://www.hca.wa.gov/hta/Documents/tympan_tubes_draft_report_073115.pdf)

Citation 20 is a draft WA HTA report on the use of tympanostomy tubes in children. The report only briefly addresses the population of children with recurrent AOM but notes that there is little evidence of efficacy or only small short-term benefits for tubes in the management of recurrent AOM. It also notes that current guidelines recommend against prescribing prophylactic antibiotics for recurrent AOM.

DRAFT

## Appendix A. Methods

### *Search Strategy*

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “otitis media,” “tonsillectomy,” “adenoidectomy,” and “tympanostomy tube.” Searches of core sources were limited to citations published after 2009.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2009.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

### *Inclusion/Exclusion Criteria*

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

# Section 4.0

## Coverage Guidance Scoring

Topic:

3D Mammography/Digital Breast Tomosynthesis for Screening Mammography						
Scoring:	Score 0	Score 1	Score 2	Score 3	Scoring	Notes
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	1	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Lever (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					60	0

Scoping notes:

**Topic:**

<b>Fecal Microbiota Transplants for C. difficile</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	1	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					45	0

**Scoping notes:**

Topic:

Genetic Tests for Selection of Antidepressant Therapy						
Scoring:	Score 0	Score 1	Score 2	Score 3	Scoring	Notes
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	1	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Lever (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					45	0

Scoping notes:

**Topic:**

<b>Interventions to Reduce the Harms of Tobacco During Pregnancy</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	2	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	Multisector interventions underutilized, variation in clinical interventions
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	3	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	3	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	3	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	3	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	2	
<b>Totals</b>					46	0

**Scoping notes:**

**Topic:**

<b>Intestinal motility tests</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	Uncertain utility not efficacy/harm
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	2	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	1	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	1	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	0	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	0	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					27	0

**Scoping notes:**

**Topic:**

<b>Long-acting reversible contraceptives</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	3	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	Due to reimbursement issues and high expulsion rate
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	3	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	3	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	2	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	3	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Lever (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					66	0

**Scoping notes:**

**Topic:**

<b>Pain Management Injection Therapies for Back Pain</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	1	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	3	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	3	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	3	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	1000 per year with imaging before and during
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	1	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	1	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Levers (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					45	0

**Scoping notes:**

**Topic:**

<b>Treatments for Recurrent Acute Otitis Media</b>						
<b>Scoring:</b>	<b>Score 0</b>	<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>	<b>Scoring</b>	<b>Notes</b>
Disease Burden (morbidity/mortality)	Inconsequential	Minor	Moderate	Major	2	
Prevalence/Population affected	Minimal	Low	Moderate	Highly prevalent	1	
Uncertain Efficacy/Harm	No controversy	Low uncertainty	Moderate	High uncertainty	2	
Variation/ Controversy	Standard Of Care in Oregon aligns w/evidence; low abuse	Little controversy/abuse/variation	Some controversy/abuse/variation	SOC differs from evidence, or frequently abused	2	
Magnitude of economic impact of intervention (population level, includes downstream costs)	No impact	Low impact	Moderate impact	High impact	2	
Potential of intervention to improve health outcomes	No impact	Minimal impact	Moderate impact	High impact	2	
Public/Professional Interest	Not in the public eye; general public would have little understanding of the issue.	Some members of the public would be interested in/aware of this topic	Frequent media coverage	Hot button issue with significant public controversy	1	
Potential of interventions to reduce health disparities	None or unknown	Low impact	Moderate impact	High impact	2	
Meaningful Coverage Guidance	No "theory of change" for how CG would increase alignment of practice/evidence	Minor change possible through promotion/precert/metrics	Moderate change possible through promotion/precert/metrics	Lever (denials, precerts, bundling, metrics) available to purchasers to align care with recommendation	3	
<b>Totals</b>					42	0

**Scoping notes:**