**MINUTES**

**Evidence-based Guidelines Subcommittee**

Clackamas Community College
Wilsonville Training Center, Rooms 111-112
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
June 2, 2016
2:00-5:00pm

---

**Members Present**: Wiley Chan, MD, Chair; Beth Westbrook, PsyD; George Waldmann, MD; Alison Little, MD, MPH, Kim Tippens, ND, MSAOM, MPH.

**Members Absent:** Eric Stecker, MD, MPH, Vice-Chair

**Staff Present:** Darren Coffman; Cat Livingston, MD, MPH; Jason Gingerich; Daphne Peck.

**Also Attending**: Adam Obley, MD, Val King MD, MPH, and Craig Mosbaek (OHSU Center for Evidence-based Policy); Jamie Hewlett and Tricia Mulcahy (Osiris); John Garrettson (Lifenet Health); Valene Marmolejo and Shannon Laney (Novadaq); Maria Rodgriguez, MD (OHSU); Barry Benson (Merck); Alejandro Perez, MD (Providence Health); Jessie Little (OHA), Kim Wentz MD, MPH (OHA).

---

**1. CALL TO ORDER**

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

---

**2. MINUTES REVIEW**

No changes were made to the 4/7/2016 minutes.

**Minutes approved 5-0**

---

**3. STAFF REPORT**

Coffman reported the decision of the HERC to limit acceptance of additional information after the formal written comment period for a coverage guidance has ended. Only in unusual circumstances ("a game changer") would additional studies be considered after the end of the formal public comment period. Waldmann asked who would make the decision whether a study met criteria for inclusion. According to the policy reviewed by HERC, staff would make this decision. Coffman said staff would keep the comment for the next 2-year review cycle. Chan asked whether staff could develop concrete criteria

DRAFT

to define a “game-changing” study. Gingerich reviewed the criteria proposed to HERC in May, acknowledging that it will be edited before being considered for adoption in August by HERC.

Livingston reviewed the topics of Coronary Artery Calcium Scoring and Coronary Computed Tomography Angiography. During the last rescan, HERC had requested that staff consider the need for revision based on a pending AHRQ report. The report has now been released and reviewed by staff. There is no need to update the topics based on the report, though they will undergo a full rescan later this year per the normal process.

Livingston also updated the subcommittee on HERC revisions to parts of the GRADE-informed framework. Changes include calculating both the number needed to treat (NNT) and absolute risk reduction (ARR) when possible. NNT would be reported only when there was a statistically significant effect. In addition, staff will use the word “confidence” in the effect column rather than “certainty.” There will also be a new row in the GRADE-informed framework making a statement about the balance of benefits and harms across outcomes.

---

**4. Skin substitutes for chronic skin ulcers**

Adam Obley reviewed the public comment disposition. There was no discussion of comments A1, B1, C1 or D1. For comment E1, there was discussion of whether to treat OASIS® Wound Matrix and OASIS® Ultra Tri-Layer Matrix as complete separate products, which could downgrade the evidence for diabetic foot ulcers (DFUs), as different products were used for each of the two trials. With only a single trial for each product, the evidence would be downgraded to very low quality, which could change the coverage recommendation. After brief discussion the subcommittee agreed to recommend both products for DFUs and retain its recommendation for OASIS® Wound Matrix for venous leg ulcers (VLUs). There was no discussion of comment G1-G6. On comment H, Chan asked about the reason for the low certainty. Obley explained that it was because of imprecision and only having 1 fair quality randomized controlled trial (RCT).

Livingston reviewed the changes in coverage recommendations as stated in the meeting materials, then invited public comment.

John Garrettson and Valene Marmolejo from from Lifenet Health gave testimony. Lifenet Health is a tissue bank that processes tissue for Dermacell. He said the company has randomized data that fulfills the requirements that staff identified. Specifically, they have a randomized controlled trial published in February 2016. He said it is a stringently done multicenter RCT. The endpoint was 100% epitheliazation and no drainage. He also said it had a more realistic conventional care arm, including several other treatments. Marmolejo also presented, noting that this is intended to be a single application product and that 75 percent of patients only required a single application. Garretson said the lead investigator was the Veteran’s Administration. He said this product could help contain costs for wound care.

In response to a question from Little about why these comments hadn’t been submitted earlier, a member of the audience from Dermacell said they were just recently told by a physician that this was under consideration.

DRAFT

Alejandro Perez provided public comment. Perez is with Providence Health and the Columbia Wound Care Consortium, a nonprofit wound care organization. He expressed concern that one of his public comments did not get considered. Perez remarked on the Zelen 2015 article comparing Epifix vs. Apligraf vs. standard of care. He said this study met FDA criteria for a good quality study. Secondly he said that the adjudication in the Zelen study was actually blinded. In addition, the Zelen 2016 study has been updated and now has 100 patients with similar findings. He then referenced Appendix E and reported that the average number of applications used in the studies was significantly lower than the coverage limits shown in the appendix. Finally, he said Epifix and Grafix come in various sizes, while use of Apligraf results in waste as it comes in only one size. He said that some of the outcomes used for the coverage guidance including quality of life and bone infection were not the intent of these skin substitutes, and that the committee set some studies up for failure. He also said that most local wound care professionals were unaware of these discussions about the draft coverage guidance.

Staff promised to investigate the issue of Perez's comment, which was submitted outside the formal public comment period. During the meeting Gingerich stated that the comment had not been forwarded to the subcommittee as it should have. *(After the meeting, staff investigated further and found that it had been treated correctly according to policy; the comment was provided to subcommittee members, though it did not receive a response in the public comment disposition because it was submitted outside the public comment period.)* Coffman asked whether there were any comments in his email were not addressed in the public comment disposition. Perez said he believed his statement that Lavery was a randomized study had not been addressed. Obley explained that staff agreed the trial was an RCT but that it had inadequate allocation concealment and that the randomization method wasn't clear. He said that the clarification from the manufacturer addressed the concern about allocation concealment but not concern about the randomization method.

Jamie Hewlett and Tricia Mulcahy from Osiris Therapeutics provided testimony. Hewlett said there was an independent clinical effectiveness review published in January 2016 where they looked at the Lavery study stating that Grafix had positive health outcomes. She also said that NICE rated Grafix highly. She said the Lavery study was a 20-center study. She also clarified that it was an independent auditor's assessment of wound closure that was included in the study (not the treating physician's assessment). All the Medicare Administrative Contractors in the United States cover Grafix. Other payers also cover Grafix. Mulcahy also noted that Grafix comes in multiple sizes, which provides cost savings. She said that in a study of 300,000 wounds, including DFUs, VLUs and pressure ulcers, comparing the costs of Apligraf and Dermagraft to Grafix, the cost was much lower with Grafix. There is a lot of waste with Apligraf and Dermagraft. Hewlett said there is another study coming out soon and asked whether it would be acceptable.

Livingston responded that in order to delay this coverage guidance further there would need to be a "game-changing" study, as discussed earlier in the meeting. The topic will be reviewed in 2 years as a matter of regular policy. Chan requested staff look at how we notify stakeholders. Coffman said we have a process where we notify certain societies when we list a topic. We also appoint an ad hoc expert to serve as a conduit for the field. Little noted that Perez was not aware though he is with a wound society. Perez said he found out later in the process. Other subcommittee members suggested increasing staff outreach to specialty societies, while acknowledging staff has limited time for outreach.

Chan said that we may need to discuss how we evaluate small studies that are too small to clearly show an effect on continuous measures (based on lack of optimal information size). Chan asked for a summary of the criteria for recommendation for or against coverage. Obley said it came down to the

DRAFT

methodologic quality of the available trials and "low" versus "very low" confidence in the strength of the estimates. Tippins asked how the subcommittee could bring the issues of waste and number of applications into the discussion. Coffman said that cost is important but that would be an additional criterion after showing effectiveness.

Waldmann asked if there could be cost information provided. Little said the costs in Appendix E appeared to be for the application, not the product itself and asked Gingerich to clarify about the costs for the product. Gingerich said that costs vary by payer. The Medicare information in the appendix depends on the setting of care. Appendix E shows product and application costs for a single application of the smallest available amount of product. He said that the cost of treatment for a patient would depend on payer arrangements, wound size, how many applications would be required as well as the setting of care. He did acknowledge that a product which was effective with a single application would be attractive from a cost perspective.

Tippins expressed reservations about not recommending Grafix and Epifix after public testimony and because of the relatively small differential in number of studies between these products and those recommended for coverage. Other subcommittee members expressed understanding of her concern, but supported the lack of recommendation for products where the assessment shows only "very low" confidence in the estimates. Some expressed hope that better studies would be available at the next scheduled review in 2 years. They also discussed that the new evidence for Dermacell would not meet the criteria discussed at the May HERC meeting as a "game changer," as there are effective alternatives for this condition. Garretson said that the product usually needs only a single application, making it different from the existing alternatives. Chan said we cannot delay the process as there are new studies coming out continually. Coffman said if the process were to be delayed it would be important to put the coverage guidance out for comment, and Livingston added that a new study might be published tomorrow for another product at that point in time. The subcommittee took a 5 minute break to allow Obley to evaluate the new Dermacell study. After the break, Livingston reported that staff evaluated the study and found it to be comparable to the other studies for this topic; it would likely receive a fair rating. However in the absence of other studies, the level of confidence in the estimate of effect would still be very low, similar to several other products not recommended for coverage. Livingston recommended moving the coverage guidance forward. After brief additional discussion, the subcommittee voted to refer the draft coverage guidance to HERC without modifications.

**Motion approved 5-0.**

### **DRAFT** 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 and Ultra Tri-Layer Matrix) | Recommended | Recommended (OASIS® Wound Matrix only) |
| EpiFix® | Not recommended | Not recommended |
| Grafix® | Not recommended | Not recommended |
| Graftjacket® | Not recommended | Not recommended |
| Omnigraft® | 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).*

---

**5. Tobacco Cessation During Pregnancy**

Obley reviewed the changes to the GRADE table, including the new formatting and the new balance of benefit and harm columns. He also reviewed the single public comment regarding high feedback ultrasound. Coffman introduced Charles Bentz, who is serving as ad hoc expert for this topic.

The subcommittee discussed the lack of a recommendation for pharmacotherapy, given the fact that the evidence does not support a health benefit from this intervention, though there is evidence it increases tobacco abstinence during pregnancy if all studies (randomized and non-randomized) are included. Livingston clarified that usually remaining silent on a recommendation is not preferred. However, in this case, federal law supercedes a coverage recommendation.

Given the lack of recommendation, Chan suggested adding language describing the evidence to the box. Westbrook asked to qualify that the evidence is insufficient only in pregnant women. Bentz said there are other important outcomes which weren't selected by the HERC for this coverage guidance, incuding

environmental outcomes. He also noted that there is unlikely to be additional evidence in this population due to ethical concerns and that he believes that pharmacotherapy along with behavioral interventions would show a clear benefit. He also raised concerns that hospitals offering nicotine replacement therapy (NRT) in a laboring woman could be adversely impacted by a non recommendation.

The subcommittee reworded the paragraph on pharmacotherapy to clarify that the evidence of the effectiveness of pharmacotherapy for critical outcomes is insufficient. They also discussed alternate language proposed by Dr. Stecker prior to the meeting.

Bentz asked to clarify that NRT would continue to be covered despite the lack of recommendation. Gingerich confirmed that Federal Law requires this coverage for pregnant women on Medicaid.

After brief additional discussion, the subcommittee voted to refer the draft coverage guidance to HERC as revised.

**Motion approved 5-0.**

### HERC DRAFT Coverage Guidance

For women who use tobacco during pregnancy, the following interventions to aid in tobacco cessation are recommended for coverage:

- Behavioral interventions (*strong recommendation*)
- Financial incentives (contingent) (*weak recommendation)*
- Prenatal ultrasound with high feedback around smoking impacts on the fetus *(weak recommendation)*

The following interventions are not recommended for coverage:

- Electronic nicotine delivery systems (strong recommendation*)*
- Counseling-based interventions to reduce secondhand smoke exposure (*weak recommendation)*
- Partner support for smoking cessation (*weak recommendation)*

Federal law requires coverage of tobacco cessation services, including FDA-approved pharmacotherapy, for pregnant women. There is insufficient evidence of effectiveness of pharmacotherapy on critical outcomes. Therefore, there is no coverage recommendation on pharmacotherapy for smoking cessation in pregnant women.

---

**5. Timing of Long-Acting Reversible Contraceptive Placement**

Coffman introduced Maria Rodruguez, appointed as ad hoc expert for this topic. King reviewed the changes to the draft coverage guidance made since the last meeting and the new ways of presenting the estimates of effect as discussed earlier.

---

The subcommittee discussed the issue of differential loss to followup in the trials. King said that there was a high loss to followup in these trials, and that it was higher in the group randomized to delayed insertion. With those women, one would not know whether they got pregnant or had complications. In the immediate group, those most likely to follow up would have been those who had expulsions or complications. In one study, 13 of 14 unintended pregnancies occurred in the delayed placement arm. Chan raised the issue that the bias could run in the opposite direction. There was an extensive methodological discussion as to whether this differential lost to followup would overestimate or underestimate the effectiveness of these methods. Rodriguez said the loss to followup is exactly what one is trying to prevent with immediate implant placement. King clarified it was not a classic as-treated analysis.

Livingston reviewed the cover letter staff drafted to accompany the coverage guidance as well as the new guidance from the Centers for Medicare and Medicaid Services (CMS) which were included in the meeting materials. The CMS guidance will be included as an appendix to the coverage guidance and the cover letter will be posted on the HERC website during the public comment period, but not as a part of what the public is invited to comment on.

Livingston asked whether anything was lacking from the bulleted list in the letter. Rodriguez said there also can be barriers within a hospital or health system which can create implementation issues. She said there is lack of awareness of availability, safety and effectiveness among patients, staff and physicians. After discussion the subcommittee added a new bullet "Lack of health system support for the uptake of policies and procedures supporting the immediate placement of LARC" to the list of barriers.

Waldmann suggested forming a workgroup to deal with the complexities of implementation. Coffman said he had heard discussion of a learning collaborative, perhaps when this coverage guidance is implemented in January. Rodruiguez said OHSU is working on a packet to provide implementation information at the hospital level. King said that in South Carolina they did very extensive training in hospitals and in outpatient facilities.

The subcommittee voted to ask staff to post the draft coverage guidance for comment as revised, and to separately post the cover letter.

**HERC Coverage Guidance**

Immediate postpartum and postabortion placement of a long-acting reversible contraceptive (LARC) (implant or intrauterine device) is recommended for coverage *(strong recommendation*).

**Motion approved 5-0.**

---

**6. ADJOURNMENT**

Livingston discussed next topics. Digital Breast Tomosynthesis (3D Mammography) for Breast Cancer Screening in Average Risk Women was up next, but may go to HTAS as HTAS will be looking at Breast

DRAFT

Cancer Screening in Women at Above-Average Risk. If that happens, the next EbGS topic will be Genetic Tests for Selection of Antidepressant Therapy.

The meeting was adjourned at 5:00 pm. The next meeting is scheduled for 9/1/2016 from 2:00-5:00 pm at Clackamas Community College, Wilsonville Training Center, Rooms 111-112, 29353 SW Town Center Loop E, Wilsonville, Oregon 97070.

DRAFT