SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

BREAST CANCER SCREENING IN WOMEN AT ABOVE-AVERAGE RISK

Population description	Women at above average age-adjusted risk of breast cancer or who have dense breasts *Population scoping notes: Includes women with pre-existing breast cancer, a personal history of breast cancer, clinically significant BRCA gene mutations (Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer, or other familial breast cancer syndromes), high-risk lesions (ductal or lobular carcinoma in situ, atypical ductal or lobular hyperplasia), or previous large doses of chest radiation therapy (≥20 Gy) before age 30 years.*
Intervention(s)	Standard digital (2-D) mammography, digital breast tomosynthesis (3-D/2-D), breast ultrasound, breast MRI, PET CT, self-exam, clinical exam, breast-specific gamma imaging, screening regimens involving combinations or alternating use of the above tests at various intervals *Intervention exclusions: None*
Comparator(s)	No screening, average risk screening regimens, comparisons of above tests to each other
Outcome(s) (up to five)	**Critical:** All-cause mortality, breast cancer morbidity **Important:** Test performance characteristics, cancer stage at diagnosis, recall rate/false-positive test results *Considered but not selected for GRADE Table: cancer-specific mortality, radiation exposure PPV for recalls, PPV for biopsies, cancer detection rate, and invasive cancer detection rate*

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Key Questions	1. What is the comparative effectiveness of enhanced strategies for breast cancer screening in women with above average risk? 2. Does the comparative effectiveness of enhanced strategies for breast cancer screening in women above average risk vary by: a. Reason for above average risk b. Age c. Race or ethnicity d. Breast density 3. What are the harms of enhanced screening strategies for breast cancer in women with above average risk? 4. What is the optimal screening interval in above-average risk women? Does the optimal screening interval vary by the: a. Characteristics listed in Key Question 2? b. Screening modality?

CHANGE LOG

Date	Change	Rationale
6/30/2016	In population description, align risk factors to exclude populations covered by the US Preventive Services Task force general requirements for screening, but specifically include women with dense breasts. Add breast-specific gamma imaging as an intervention. Change references to 'adults' to 'women' throughout. Align outcomes with separate coverage guidance for digital breast tomosynthesis (DBT) for consistency. Align outcome scoping notes with changes in the population regarding prior ductal carcinoma in situ. Include breast cancer morbidity rather than cancer-specific mortality. Align key questions with coverage guidance on DBT, and treat breast density as a factor which may affect effectiveness.	Revisions to align this coverage guidance with the scope statement for the coverage guidance on digital breast tomosynthesis and recommendations from the United States Preventive Services Task Force (USPSTF). Clarify references to digital breast tomosynthesis, that they would be used in conjunction with 2-D images. Clarify treatment of dense breasts.

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SCOPE STATEMENT FOR HERC COVERAGE GUIDANCE

DIGITAL BREAST TOMOSYNTHESIS (3-D MAMMOGRAPHY) FOR BREAST CANCER SCREENING IN AVERAGE RISK WOMEN

Population description	Women between the ages of 40 and 74 years referred for breast cancer screening *Population scoping notes: Excludes women with a personal history of breast cancer, clinically significant BRCA gene mutations, Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer or other familial breast cancer syndromes, high-risk lesions (ductal or lobular carcinoma in situ, atypical ductal or lobular hyperplasia), or previous large doses of chest radiation therapy (≥20 Gy) before age 30 years.*
Intervention(s)	Digital breast tomosynthesis (3-D mammography) in conjunction with standard 2-D digital mammography *Intervention exclusions: None*
Comparator(s)	Standard 2-D mammography with or without computer-aided diagnosis *Considered but not selected: No screening, MRI, ultrasound*
Outcome(s) (up to five)	Critical: All-cause mortality, breast cancer morbidity Important: Test performance characteristics, cancer stage at diagnosis, recall rate/false positive test results *Considered but not selected for GRADE Table: cancer-specific mortality, radiation exposure PPV for recalls, PPV for biopsies, cancer detection rate, and invasive cancer detection rate*

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Key Questions	1. What is the comparative effectiveness of digital breast tomosynthesis (DBT) as a primary screening modality in women referred for breast cancer screening? 2. Does the comparative effectiveness of DBT vary by the following characteristics: a. Age b. Race or ethnicity c. Breast density 3. In a screening population, how do the test characteristics of 3-D/2-D mammography compare to those of standard 2-D mammography? 4. What are the harms of 3-D/2-D mammography compared to standard 2-D mammography alone? 5. If DBT is used as a primary screening modality, what is the optimal screening interval, and does that interval vary according to the characteristics listed in Key Question 2?

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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.
6/27/2016	Aligned population scoping notes to match US Preventive Services Task Force (USPSTF) definitions of average risk population. Changed outcomes to align with separate planned coverage guidance on breast cancer screening for women at above-average risk. Add race and ethnicity to the characteristics examined. Break the discussion of screening intervals into a separate key question, #4.	Align with USPSTF population, as coverage of mammography in general is governed by this definition. Align coverage guidances so that they do not overlap and cover the necessary subject area.

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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).

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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

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

Minutes approved 5-0

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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

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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.

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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.

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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

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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).*

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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.

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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 methodogical 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.

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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.

Motion approved 5-0.

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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 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.

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