Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Noninvasive Diagnostic Techniques for the Detection of Skin Cancers

Draft review available for public comment from May 05, 2011 to June 02, 2011.

Research Review Citation: Parsons, S.K., Chan, J.A., Yu, W.W., Obadan, N., Ratichek, S.J., Lee, J., Sen, S., Ip S. Noninvasive Diagnostic Techniques for the Detection of Skin Cancers. Technical Brief No. 11. (Prepared by the Tufts University Evidence-based Practice Center under Contract No. 290-2007-1055-1.) AHRQ Publication No. 11-EHC085-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

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

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Introduction	Well done. Nothing to add.	Thank you.
Peer Reviewer 2	Introduction	Yes	No response needed.
Peer Reviewer 2	Introduction	This is all good. In the framework flow chart there are some wiggly lines and I am not sure what these represent or if they are necessary.	In our AF, solid wiggly lines generally indicate associations/relationships that are present, but not direct or not of our interest. They can be impact of effect modifiers, or adverse effects of interventions. The dotted wiggly line between the noninvasive test box and the biopsy box indicates that we were comparing between the two tests.
Peer Reviewer 3	Methods	Methods might want to specify if epublished articles were included in the search—apparently not because the review is missing major article published online in Feb 2011 on MelaFind: ONLINE FIRST The Performance of MelaFind A Prospective Multicenter Study Gary Monheit, MD; Armand B. Cognetta, MD; Laura Ferris, MD, PhD; Harold Rabinovitz, MD; Kenneth Gross, MD; Mary Martini, MD; James M. Grichnik, MD, PhD; Martin Mihm, MD; Victor G. Prieto, MD, PhD; Paul Googe, MD; Roy King, MD; Alicia Toledano, ScD; Nikolai Kabelev, BCSc; Maciej Wojton, MS; Dina Gutkowicz-Krusin, PhD Arch Dermatol. 2011;147(2):188-194. doi:10.1001/archdermatol.2010.302	We did not do a pre-Medline search, but we are aware of this study from ClinicalTrials.gov (see Appendix C, Table C2). A description of MelaFind is now included in a new (and separate) section, entitled, "Multispectral imaging and fully automated computer-based analysis." The Monheit citation has also been added to the final number of abstracts reviewed in this technical brief.
Peer Reviewer 1	Methods	Are the inclusion and exclusion criteria justifiable? YES Are the search strategies explicitly stated and logical? YES Are the definitions or diagnostic criteria for the outcome measures appropriate? YES Are the statistical methods used appropriate? YES	No response needed.
Peer Reviewer 2	Methods	Yes	No response needed.
Peer Reviewer 2	Methods	Inclusions of type of study may be too inclusive with case reports and none comparative cohorts and technical reports contributing little to the overall analysis / synthesis of findings	Given the relatively paucity of information, we felt that the full description of the evidence base would be helpful to the reader.

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Peer Reviewer 3	Results	The measured sensitivity of MelaFind was 98.4% (125 of 127 melanomas) with a 95% lower confidence bound at 95.6% and a biopsy ratio of 10.8:1; the average biopsy sensitivity of dermatologists was 78% in the reader study. Including borderline lesions (high-grade dysplastic nevi, atypical melanocytic proliferations, or hyperplasias), MelaFind's sensitivity was 98.3% (172 of 175), with a biopsy ratio of 7.6:1. On lesions biopsied mostly to rule out melanoma, MelaFind's average specificity (9.9%) was superior to that of clinicians (3.7%) (P = .02).	This study is now cited in the report.
Peer Reviewer 1	Results	Is the amount of detail presented in the results section appropriate? YES Are the characteristics of the studies clearly described? YES Are the key messages explicit and applicable? YES Are figures, tables and appendices adequate and descriptive? YES Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? NO	No response needed.
Peer Reviewer 2	Results	Yes	No response needed.
Peer Reviewer 2	Results	Amount of detail is appropriate	No response needed.
Peer Reviewer 1	Discussion/ Conclusion	Are the implications of the major findings clearly stated? YES Are the limitations of the review/studies described adequately? YES In the discussion, did the investigators omit any important literature? NO Is the future research section clear and easily translated into new research? YES	No response needed.
Peer Reviewer 2	Discussion/ Conclusion	Yes	No response needed
Peer Reviewer 2	Discussion/ Conclusion	All pretty clear. In the future steps text is a little discursive and some key points to future research questions would be helpful particularly in the type of studies that would be most informative - diagnosis against gold standard - impact on improved detection or selection of cases. Many of the experimental methods seem to lack any good evidence to recommend their introduction with exception of dermoscopy and confocal microscopy. Perhaps more emphasis on improving existing technology and its evidence base rather than trying to develop new technology would be more productive although the reasons for this are likely profit / commerce	To address this issue, we did a substantial re-write of the existing technology section, notably dermoscopy.

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Peer Reviewer 3	Conclusion	MelaFind is a safe and effective tool to assist in the evaluation of pigmented skin lesions. Trial Registration clinicaltrials.gov Identifier: NCT00434057 3. The photography section might consider adding the Canfield Visia and other UV photography systems. 4. Topical therapies for skin cancer—e.g. imiquimod and 5-FU could be used in combination with photography to highlight skin cancers.	This device is now included in a new section, entitled "Multispectral imaging and fully automated computer-based analysis." 3. UV photography is described under PDD, Variations of Technique, and referenced in the. 4. Although the report does not cover PDT (photodynamic therapy), these agents have been included under Variations of Technique in the PDD section.
Peer Reviewer 3	General	Comprehensive well done technical brief.	No response needed.
Peer Reviewer 1	General	Is the report clinically meaningful? YES Are the target population and audience explicitly defined? YES Are the key questions appropriate and explicitly stated? YES	No response needed.
Peer Reviewer 2	General	Yes	No response needed.
Peer Reviewer 2	General	The target population is not clearly defined - is this dermatologists, health care providers / insurers of industry perhaps all of these? It may be that this is more for American readers with FDA emphasis and setting and descriptors of current American practice. The questions are clearly described and appropriate	The target audience is all interested parties.
Peer Reviewer 4	General	This is a clinically relevant report of the state of the art in non-invasive techniques of skin tumors (suspicious lesions). The target population is well-defined and the key questions adequately stated. Some suggestions, changes and points need to be clarified by the authors (see attached document)	Comments have been reviewed as detailed below.
Joseph Gulfo, MD. President & CEO, MELA Sciences, Inc.	General	Contrary to its description in the draft technical brief, 1 MelaFind~ is not a dermoscope. A dermoscope is a device that requires subjective analysis by the user. The draft report correctly observes, "The level of training and experience of the user may well determine the effectiveness of dermoscopy: 2 In contrast, MelaFind® is an objective tool; it is a non-invasive, multispectral, objective computer vision system for early melanoma detection. Moreover, as the draft report notes, dermoscopes are approved by the FDA as Class I or Class II devices,3 but MelaFind® is being reviewed by the FDA as a Class III device. MelaFind® is a unique device and should not be evaluated in the same section of the report as dermoscopes. We recommend that a new section be added to the technical brief to discuss "devices under investigation," including MelaFind.	Thank you. A section on this device has been added to the report.

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		In addition, the draft report cites a third-party press release from May 2010 for information about the false positive rate associated with the MelaFind® device,' instead of the published, peer-reviewed pivotal study. This prospective, multicenter, blinded study, published in the Archives of Dermatology, found that "MelaFind® is a safe and effective tool to assist in the evaluation of pigmented skin lesions: 5 The measured sensitivity of MelaFin~ was 98.4%.6 "For lesions that were not melanomas and had prebiopsy diagnoses of melanoma cannot be ruled out or not melanoma, MelaFind had an average specificity of 9.5%, ie, significantly higher than that of investigators (3.7%) (P=.02).·7 Attached is a copy of this study for your consideration as you revise the technical brief.	
Peer Reviewer 1	Clarity and Usability	Is the report well structured and organized? YES Are the main points clearly presented? YES Can the conclusions be used to inform policy and/or practice decisions? YES	No response needed.
Peer Reviewer 2	Clarity and Usability	Yes	No response needed.
Peer Reviewer 2	Clarity and Usability	Amongst harms there is a potential for technology to displace the important role of the trained dermatologist. we see this in my country with high street technicians offering screening and coming up with different advice than the specialist.	This is an interesting comment. We have not formally addressed it in the report, but certainly appreciate the concern.
Peer Reviewer 4	Clarity and Usability	The report is well structured and organised. The conclusions need changes (see file attached). They may be used to inform policy and/or practice decisions.	The comments have been reviewed and incorporated in the appropriate sections.
Peer Reviewer 4	Background	See evidenced based guidelines of Melanoma in Australia and New Zealand (http://www.nhmrc.gov.au/publications/synopses/cp111syn.htm), European Guidelines (Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Spatz A, Grob JJ, Malvehy J, Newton-Bishop J, Stratigos A, Pehamberger H, Eggermont A. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary Guidelines. Eur J Cancer. 2010 Jan;46(2):270-83)	Because the focus of our search was not melanoma screening and detection, we did not identify these guidelines. We have included them in the background section of the report. Thank you.
Peer Reviewer 4	Results	The dermoscope is a magnifying lens equipped with polarised light source… Comment: A dermatoscope can use polarised light or non polarised light. Please correct.	Corrected. Thank you.
Peer Reviewer 4	Methods	Key informants should disclose conflicts of interest.	All key informants completed conflict of interest forms. This information is now included in the report.
Peer Reviewer 4	Results	In correlation study between polarised and non polarised dermoscopy it was seen that there was excellent agreement for overall dermoscopic patterns between modalities, with kappa values	This citation has been added to the report. Thank you.

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		ranging from 0.88 to 1.00. (Benvenuto-Andrade C, Dusza SW, Agero AL, Scope A, Rajadhyaksha M, Halpern AC, Marghoob AA.Differences between polarized light dermoscopy and immersion contact dermoscopy for the evaluation of skin lesions.Arch Dermatol. 2007 Mar;143(3):329-38)	
Peer Reviewer 4	Results	Kittler H, Guitera P, Riedl E, Avramidis M, Teban L, Fiebiger M, Weger RA, Dawid M, Menzies S.Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging.Arch Dermatol. 2006 Sep;142(9):1113-9.	This citation is already included in the draft.
Peer Reviewer 4	Results	Malvehy J, Puig S, Martí-Laborda RM. Dermoscopy of skin lesions in two patients with xeroderma pigmentosum. Br J Dermatol. 2005 Feb;152(2):271-8.	This citation from our database has been added to the list of included studies.
Peer Reviewer 4	Results	Puig S, Malvehy J, Badenas C, Ruiz A, Jimenez D, Cuellar F, Azon A, Gonzàlez U, Castel T, Campoy A, Herrero J, Martí R, Brunet-Vidal J, Milà M. Role of the CDKN2A locus in patients with multiple primary melanomas. J Clin Oncol. 2005 May 1;23(13):3043-51.	Gene locus study was not included in this brief.
Peer Reviewer 4	Results	The performance of a decision-support system for melanoma diagnosis under real-life conditions is lower than that expected from experimental data and depends upon the physicians who are using the system because they may not choose the correct lesion to be analysed. (Dreiseitl S, Binder M, Hable K, Kittler H. Computer versus human diagnosis of melanoma: evaluation of the feasibility of an automated diagnostic system in a prospective clinical trial. Melanoma Res. 2009 Jun;19(3):180-4)	Stand-alone computer system was not included in this report.
Peer Reviewer 4	Results	Two different metanalyses showed the increased accuracy of dermoscopy versus naked eye examination in the detection of melanoma. This was considered first level evidence in several guidelines of melanoma. Survival impact in the diagnostic interventions are not established in most of the dermatological diagnostic techniques including melanoma, most probably because studies might not be considered ethical or might not able to be conducted with an adequate design at an adequate cost. It seems that some evidence in the reduction of unnecessary biopsies of benign lesions with reduction of morbidity can be concluded from studies including one RCT. A very significant impact in the adequacy of referral of suspicious lesions by primary care physicians was concluded by one RCT study. The actual conduct of dermoscopy as practiced in the US dermatology setting must be quite heterogeneous owing to the different available algorithms…Comments: this algorithms are all valid in terms of diagnostic accuracy and reproducibility. The authors conclude that “it would not be easy to confidently discern the benefits	We did not critically examine these two meta-analyses. However, they are based on the same observational studies tabulated in our report. Anyhow, to state a conclusion about the effectiveness of dermoscopy is beyond the scope of this technical brief. However, we agreed and have deleted our “opinion” from this brief.

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		of dermoscopy based on observational studies alone" in US. This is an opinion by the authors that it is not based in objective data.	
Peer Reviewer 4	Results and Background (guidelines)	Comments: Randomization of two groups of high-risk patients for melanoma with and without dermoscopy will not be ethically accepted since evidence of superiority of dermoscopy in melanoma diagnosis has been proven. Mention the RCT studies with positive results in dermoscopy and the two metaanalyses published. Also include comment on dermoscopy as recommended in the examination of patients with suspicious skin tumours by the Melanoma European guidelines (Garbe et al) and The Australian and New Zealand evidence based guidelines. Training on dermoscopy with 4 hours course was able to significantly improve the suspicious tumours detection in one RCT study (Argenziano G, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006 Apr 20;24(12):1877-82.)	Even if the superiority of dermoscopy has been proven, it does not necessarily mean that adopting its use will automatically lead to improved health outcomes as that could depend on other factors as well. To critically appraise the different guidelines is beyond the scope of this brief. We have referenced the 2009 Guidelines Synthesis from the US National Guideline Clearinghouse. Guidelines are now referenced in the background section.
Peer Reviewer 4	Results	A CSE aided by dermoscopy takes significantly longer than a CSE without dermoscopy. However, a thorough CSE, with or without dermoscopy, requires less than 3 minutes, which is a reasonable amount of added time to potentially prevent the morbidity and mortality associated with skin cancer"	This comment has been added to the brief.
Peer Reviewer 4	Results	Concerns of nosocomial transmission by dermoscopy can only be considered for old devices with contact dermoscopy that used mineral oil as an immersion fluid. Today most contact dermatoscopists use alcohol.	This has been added to the brief.
Peer Reviewer 4	Results	Dermoscopy could be used to help improve the diagnosis of skin tumours including melanocytic and non-melanocytic tumours.	This has been added to the brief.
Peer Reviewer 4	Results	Terushkin V, Oliveria SA, Marghoob AA, Halpern AC. Use of and beliefs about total body photography and dermatoscopy among US dermatology training programs: an update. J Am Acad Dermatol. 2010 May;62(5):794-803.	This has already been included in the TBP section. We have added the data on dermoscopy to the dermoscopy section.
Peer Reviewer 4	N/A	Cost of dermoscopy without image capture is form 150-1000 dollars Cost of dermoscopy with image capture ranges between 6000 and 40000 dollars	While we found this information to be very interesting, inclusion of cost estimates of these devices is outside of the scope of the brief.
Peer Reviewer 4	Results	Confocal microscopy; Theoretical advantages (p. 28) Several studies in lentigo maligna melanoma, amelanotic melanoma and diagnostic accuracy in equivocal lesions by dermatoscopy pointed out the clinical use of confocal microscopy in the examination of suspicious lesions.	These studies have been added to this section. We had previously identified them in our master search.

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		Guitera P et al. The impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. J Invest Dermatol. 2010 Aug;130(8):2080-91. Guitera P et al. In vivo reflectance confocal microscopy enhances secondary evaluation of melanocytic lesions.J Invest Dermatol. 2009 Jan;129(1):131-8. Pellacani G et al. The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions. J Invest Dermatol. 2007 Dec;127(12):2759-65. Segura S et al. Development of a two-step method for the diagnosis of melanoma by reflectance confocal microscopy. J Am Acad Dermatol. 2009 Aug;61(2):216-29.	
Peer Reviewer 4	Results	Theoretical disadvantages of confocal microscopy Bulky devices are now replaced by hand held confocal. Confocal microscopy cannot replace histopathological diagnoses.	We have added reference to the hand held devices in the description of the technique.
Peer Reviewer 4	Results	Ultrasound/Laser Doppler/Description of technique Cite the paper by Seidenari and Pellacani and Vilana R et al. Guitera P et al. Melanoma histological Breslow thickness predicted by 75-MHz ultrasonography.Br J Dermatol. 2008 Aug;159(2):364-9.	These have been added as examples of use in presurgical planning.
Peer Reviewer 4	Results	Theoretical advantages A retrospective study comparing ultrasound diagnoses with clinical diagnoses Comment should be ….ultrasound diagnoses with clinical diagnoses versus clinical diagnoses alone…	This wording has been changed.
Peer Reviewer 4	Results	Tape stripping (page 35) Cite paper by Wachsman W et al. Noninvasive genomic detection of melanoma. *Br J Dermatol. 2011 Apr;164(4):797-806)*	Although this article was published outside of our search dates (published April 2011), we have included it because of its relevance. Table 5 has been updated to reflect the additional study on test accuracy.