Evidence-based Practice Center Technical Brief Protocol

Project Title: Technical Brief - Evaluation of Suspicious Skin Lesions Using Non-Invasive Diagnostic Techniques

I. Background and Objectives for the Technical Brief

Cancers of the skin are the most common forms of cancer in men and women, accounting for nearly half of all malignancies. In 2009 more than 1 million cases were expected in the US,[1] predominantly basal cell or squamous cell in origin. These two types of nonmelanomatous (NMSC) lesions, responsible for more than 800,000 cases per year, are associated with aging and sun exposure. Recent studies have also linked NMSC to prior cancer therapy, especially radiation therapy.[2] Additionally, while NMSC is rarely lethal, these lesions are associated with other malignancies.[3] In contrast, melanoma accounts for approximately 4% of all skin cancer cases, but causes the majority of skin cancer deaths.[4] One study found that "melanoma incidence rates had doubled in all socioeconomic groups over a 10-year period".[5] Another study found that melanoma incidence rates have increased by 3% per year in white Hispanic and white non-Hispanic population, and both white Hispanic and blacks had more advanced disease at presentation.[6] Melanoma also has significant morbidity and late stage melanoma has significant mortality.[7, 8]

At present, it does not appear that there are consistent guidelines for assessment of suspicious skin lesions, particularly those at risk for primary or recurrent disease. The lack of consistent guidelines notwithstanding, according to Goodson and Grossman, most dermatologists would agree that the goals for monitoring of nevi and detection of melanoma include the identification of high-risk patients, early biopsy of melanomas, observation of nevi, and the avoidance of unnecessary biopsies.[9] High-risk patients in the case of melanoma include those patients with a personal history, family history, suspicious skin lesions (e.g., atypical nevi), and other risk factors (e.g., age ≥50 years, prior history of cancer).

The assessment of a suspicious skin lesion typically begins with a physical examination and inspection of the skin. Many dermatologists use dermoscopy (also known as dermatoscopy epiluminescence microscopy or surface microscopy) to better examine the lesion. The dermoscope is a magnifying lens with a light source which is held near the suspicious lesion. Confocal microscopy is primarily used in research centers, while full body and digital photography are used across practice settings and specialty groups. Some of these devices have been approved or cleared by the FDA; others are in general use (e.g., photography). In addition, a number of imaging modalities are emerging to help improve the diagnostic accuracy of visual inspection of pigmented skin lesions. These include epidermal genetic tape stripping, "scent"/"odor", ultraviolet photography, fluorescence, ultrasound, laser Doppler, bio-electrical impedance, polarized light photography, 3-D histograms of color mapping, and thermography.[10]

The objective of this technical brief is to examine how these emerging non-invasive imaging modalities could be used to help diagnose cancerous tumors of the skin. While the focus of the brief will be on those modalities currently in use and/or FDA approved or cleared, we will

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consider future technologies, based on available data and input from our Technical Expert Panel as to the potential importance of these technologies and where they might fit into the care process. We will also examine whether there are indications of differing effectiveness among techniques for early detection of skin cancers among whites, blacks, and Hispanics and if that should be a focus of future comparative effectiveness research. We will stratify the findings by whether the patients had previous history of skin cancer or not and whether or not patients have a history of other malignancies. The rationale for this is the growing recognition of skin cancer as a leading form of second malignancy.[2, 3]

II. Guiding Questions

Guiding question 1:

What are the different non-invasive techniques/modalities that have been proposed to be used for the early detection of skin cancer?

a. What are the postulated advantages and disadvantages of these non-invasive diagnostic techniques compared to biopsy, among individuals who should be considered for these technologies?

b. What are the potential safety issues and harms associated with the use of non-invasive diagnostic techniques for the evaluation of suspicious skin lesions?

c. What is the current FDA clearance status of these modalities?

d. What kinds of training and certifications are needed to use these techniques/modalities?

e. What are some of the newer techniques/modalities in development?

Guiding question 2:

What is the current clinical context in which these new non-invasive modalities are used – who uses them, in what setting, for which cancers, with which patients?

a. Are there reasons to consider that some techniques may be more or less effective for the early detection of skin cancers in those patients who had a previous history of skin cancer, previous history of any cancer, or no history of cancer?

b. Are there reasons to consider that some techniques may be more or less effective for the early detection of skin cancers among whites, blacks, and Hispanics?

Guiding question 3:

What published and unpublished studies have reported on the use and safety of these non-invasive modalities? Provide a synthesis of the following information:

i Indication/patient inclusion criteria

ii Type of techniques/modalities

iii Study design and size

iv Role of the test in patient management

v Setting where the technique/modality was used

vi Outcomes assessed

vii Adverse events, harms and safety issues reported

viii Comparators used (applicable only to comparative studies)

ix Length of follow-up (applicable only to longitudinal studies)

Guiding question 4:

What is the projected diffusion of these different techniques/modalities in the near future? What are potential areas for future research that are most meaningful given the current state of the evidence and the projected diffusion of these techniques/modalities?

III. Methods

1. Data Collection:

A. Discussions with Key Informants

A representative panel of Key Informants, referred to in this phase of the project as Technical Experts, has been identified through the previous Topic Refinement process. These individuals include medical experts/practitioners in dermatology, oncology, and family medicine, as well as scientists and representatives of professional societies. Additional individuals may be added as necessary, according to information collected during the course of research.

Technical experts will be collectively, where appropriate, and individually (if necessary) interviewed for their responses to Guiding Questions 1, 2 and 4. Interview questions will be tailored to the unique perspective and expertise of each Technical expert. Interviews may be recorded with the permission of the Technical Expert, exclusively the purpose of accurate representation of the interview content. Any recorded interviews will be destroyed following completion of the Technical Brief.

B. Grey Literature search

For Key Questions 1, 2 and 4, we will perform an Internet search for keywords to identify the newer non-invasive techniques/modalities not in current use, such as fluorescence, high-resolution ultrasound, laser Doppler, bio-electrical impedance, polarized light photography, 3-D histograms of color mapping, and thermography. For these searches, unless otherwise advised, we intend to use the Google search engine and for each search string entered we will peruse the first 10 pages to identify relevant links. We acknowledge that open-ended searches of the Internet (including "Google searches") are challenging and often not strictly reproducible. The most relevant links are often ranked differently even if the searches are done in close proximity to each other using the exact same search terms. Perusing the first 10 pages (versus the first 1 to 2 pages) could help lessen the chance of missing important and relevant links.

We will also search major vendors/manufacturers' websites for information pertaining to the different non-invasive modalities. To identify major vendors/manufacturers and to obtain FDA clearance status of relevant devices, we will search the FDA Center for Devices and Radiological Health (CDRH) database. Since this search process requires the name of the device, rather than just the device category, we will consult our Technical Experts to ensure that we compile the most comprehensive list possible.

For potential harms with the relevant devices, we will query the FDA Manufacturer and User Facility Device Experience (MAUDE) database for any reported harms with the use of the relevant devices.

We will also search ClinicalTrials.gov for any ongoing relevant trials involving the various non-invasive modalities of interest.

C. Published Literature search

We will search the Medline. We plan to restrict our search to literature published within the last 10 years as the modalities of interest are all fairly new. We will supplement our literature search with suggestions from technical experts as well as review articles and manufacturers' documents. Box 1 summarizes our proposed eligibility criteria for selecting literature to be included in this technical brief. Both literature search strategy and eligibility criteria will be modified based on inputs from the Key Informants.

Data to be abstracted for answering Guiding Question 3 are described in section III.2.

We do not foresee the need for updated literature searches, as this is a project that will be completed in a relatively short time frame (7 months or earlier).

Box 1. Proposed eligibility criteria

Population(s)

- all patients regardless of age, race, and sex
- patients with new suspicious lesions or recurrent

Interventions

- Dermoscopy
- Confocal microscopy
- Full body photography
- Digital Photography
- Other non-invasive technologies for which outcomes are available

Outcomes

- Probability/prevalence of early detection of skin cancer
- Sensitivity and specificity of the non-invasive diagnostic technique
- Detection of new lesions that would otherwise have been delayed or not detected
- Probability/prevalence of unnecessary biopsies
- Reduction of harms (disfigurement, misdiagnoses, side effects, cost, heightened surveillance) induced by unnecessary biopsies
- Quality of life
- Anxiety
- Skin cancer survival
- Overall survival

Setting

- Outpatient setting in either the primary care or specialist's office

2. Data Organization and Presentation:

A. Information Management, and Database Generation and Software

The EPC has developed specialized software (*Abstrackr* –beta) to facilitate abstract screening. The software will be used to provide a user interface that will allow the investigators to easily accept and reject abstracts on screen and track the selection process. The first few hundred (200-300) citations will be screened jointly by all investigators to ensure that screening criteria are well understood and applied uniformly. Thereafter, investigators will screen non-overlapping sets of the remaining citations.

For studies identified through the Literature Search, we will extract information on items of interest (PICOS) including information specific to the particular non-invasive modality using customized forms. From qualified studies, we will extract data on the citation (first author name, journal and year of publication), study design, condition being evaluated,

study size and setting, and particular non-invasive modality. We will also record details relevant to the technical specification of the particular non-invasive modality. We will also record the outcomes being assessed in each study, including harms related to the particular non-invasive testing.

Relevant inputs from Technical Expert interviews will be integrated with information obtained through the published and grey literature sources.

B. Data Presentation

We will generate tables (evidence map) summarizing items relevant to Guiding Question 3. We will calculate summary descriptive statistics in the eligible studies such as proportions (e.g., of studies with a specific characteristic), or medians and interquartile range (e.g., for study sample sizes), when appropriate.

Each non-invasive modality will have a descriptive qualitative synthesis using information gathered for Guiding Questions 1 and 2. These descriptive syntheses may be supplemented with tables and graphs to facilitate comprehension of the extracted data.

To answer Guiding Question 4, we will make semi-quantitative projection of the various non-invasive modalities uptake and identify the knowledge gaps based on the extracted data and thereby note potential areas of future research.

IV. References

(1) Cancer Facts & Figures 2009. Atlanta: American Cancer Society; 2009.

(2) Perkins JL, Liu Y, Mitby PA et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2005 June 1;23(16):3733-41.

(3) Rosenberg CA, Greenland P, Khandekar J, Loar A, Ascensao J, Lopez AM. Association of nonmelanoma skin cancer with second malignancy. *Cancer* 2004 January 1;100(1):130-8.

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(5) Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. *J Invest Dermatol* 2009 July;129(7):1666-74.

(6) Hu S, Parmet Y, Allen G et al. Disparity in melanoma: a trend analysis of melanoma incidence and stage at diagnosis among whites, Hispanics, and blacks in Florida. *Arch Dermatol* 2009 December;145(12):1369-74.

(7) Gloster HM, Jr., Brodland DG. The epidemiology of skin cancer. *Dermatol Surg* 1996 March;22(3):217-26.

(8) Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med* 2004 September 2;351(10):998-1012.

(9) Goodson AG, Grossman D. Strategies for early melanoma detection: Approaches to the patient with nevi. *J Am Acad Dermatol* 2009 May;60(5):719-35.

(10) Terushkin V, Halpern AC. Melanoma early detection. *Hematol Oncol Clin North Am* 2009 June;23(3):481-500, viii.

V. Definition of Terms

Not applicable.