Diagnostic test accuracy for skin cancer project:
Implications for practice and research

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Rough plan

- What did we do?
- Why did we do it?
- How did we do it?
- What did we find?
- What does it all mean?
- Lessons I learned?
Conflicts of interest and funding

- I work for the NHS
- I work for the NIHR HTA
- I have no financial or research associations with any of the diagnostic technologies assessed

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Diagnosing skin cancer

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Early and accurate detection of all skin cancer types is essential for its appropriate management, reduction of morbidity, and improvement in survival rates. There are three main forms of skin cancer. Melanoma and cutaneous squamous cell carcinoma (cSCC), are high-risk skin cancers with the potential to metastasise, and ultimately lead to death. A basal cell carcinoma (BCC) rarely metastasises, usually remaining localised with potential to infiltrate and damage surrounding tissues. BCCs and cSCCs are also referred to as keratinocyte skin cancers.

The aim of any testing for skin cancer is to detect all possibly malignant cases using high sensitivity techniques, without having too many false positives, which lead to unnecessary referrals. There is a trade-off between sensitivity and specificity, as techniques with high sensitivity lead to lower specificity (a higher number of false positives). With increasing rates of skin cancer worldwide [1, 2], and a trend to adopt dermoscopy, and other high-resolution image analysis in primary care, anxiety around missing identification of early malignant lesions needs to be balanced against the risk of unnecessary referrals to specialists.

If additional testing is used in primary care to make sure that potentially malignant lesions are detected, there is a risk that the number of people with benign skin conditions who are referred unnecessarily to specialist care will increase. It is important, therefore, that tests should be evaluated in the settings in which they will be used in practice.

Sophisticated techniques from specialist settings, need to be assessed in terms of their ability to diagnose more difficult cases, and whether they can reduce unnecessary excisions.

The Cochrane Reviews in this Special Collection focus on diagnosis of cutaneous melanoma, keratinocyte skin cancer and all types of skin cancer. This collection brings together a series of new diagnostic test accuracy systematic reviews for diagnosing skin cancer, which aim to identify the most accurate approaches to diagnosis, and so provide the best evidence on which clinical and policy-related decisions can be based. The reviews have been conducted by the Cochrane Skin Group. They have been led by Dr Jac Dinnes, and funded by the UK National Institute for Health Research.

Diagnosis of cutaneous melanoma

Visual inspection for diagnosing cutaneous melanoma in adults

History-taking and visual inspection of a suspicious lesion by a clinician is usually the first in a series of tests to diagnose skin cancer. This review aims to determine the diagnostic accuracy of visual inspection for the detection of cutaneous invasive melanoma and intraepidermal melanocytic variants in adults with limited prior testing, and in those referred for further evaluation of a suspicious lesion.
But first a diagnostic test for you:

What are these lesions called?
Dear Doctor, please would you see this patient with a _ _ mole
Plan

- What did we do?
  - Why did we do it?
  - How did we do it?
  - What did we find?
  - What does it all mean?
  - Lessons I learned?
Topics covered: melanoma

- Visual inspection for diagnosing cutaneous melanoma in adults
- Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults
- Reflectance confocal microscopy for diagnosing cutaneous melanoma in adults
- Smartphone applications for triaging adults with skin lesions that are suspicious for melanoma

(Staging for melanoma out for review)
Keratinocyte skin cancer - basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC)

- Visual inspection and dermoscopy, alone or in combination, for diagnosing keratinocyte skin cancers in adults

- Reflectance confocal microscopy for diagnosing keratinocyte skin cancers in adults

- Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults
Topics Covered: diagnosis of skin cancers including melanoma, BCC and cSCC

- **Teledermatology** for diagnosing skin cancer in adults
- **Computer-assisted diagnosis techniques** (dermoscopy and spectroscopy-based) for diagnosing skin cancer in adults
- **High-frequency ultrasound** for diagnosing skin cancer in adults
- **Optical coherence tomography** for diagnosing skin cancer in adults
Sensitivity and specificity
Sensitivity & specificity: trade-off requirement will vary
Why did we do it?

- **Need** – expanding use of technologies and NICE guidelines
- **Opportunity** for Cochrane Skin to expand skills into DTA reviews with Birmingham
- **Patient benefit** – promote well evidenced practice and demote dodgy technologies
- **Money and prestige?** – nearly killed us
Clear question: To determine the diagnostic accuracy of dermoscopy alone, or when added to visual inspection of a skin lesion, for the detection of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults. We separated studies according to whether the diagnosis was recorded face-to-face (in-person), or based on remote (image-based), assessment.
Searches

- Following databases from inception up to August 2016: CENTRAL; MEDLINE; Embase; CINAHL; CPCI; Zetoc; Science Citation Index; US National Institutes of Health Ongoing Trials Register; NIHR Clinical Research Network Portfolio Database; and the World Health Organization International Clinical Trials Registry Platform.

- Plus reference lists and published systematic review articles.
Selection criteria

- Studies of any design that evaluated dermoscopy in adults with lesions suspicious for melanoma, compared with a reference standard of either histological confirmation or clinical follow-up. Data on the accuracy of visual inspection, to allow comparisons of tests, was included only if reported in the included studies of dermoscopy.
Data extraction

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). We contacted authors of included studies where information related to the target condition or diagnostic threshold were missing.
Classical DTA biases for skin cancer

- **Incorporation bias** – gold standard (histopath) incorporates index test or index test known to gold standard

- **Partial verification bias** – those with +ve index test more likely to get histopath and only those who get histopath reported in study

- **Differential verification bias** – only those with +ve index test get immediate histology. Others have clinical follow-up

- **Imperfect gold standard** – histopath?
Data analysis

- Estimated accuracy using hierarchical summary receiver operating characteristic methods (SROC)
- Analysis of studies allowing direct comparison between tests was done.
- Computed values of sensitivity at the point on the SROC curve with 80% fixed specificity and values of specificity with 80% fixed sensitivity. Investigated impact of in-person test interpretation using developed algorithms; observer expertise; and dermoscopy training
Plan

- What did we do?
- Why did we do it?
- How did we do it?
- **What did we find?**
  - What does it all mean?
  - Lessons I learned?
5. Risk of bias and applicability concerns graph for in-person evaluations: review authors’ judgements about each domain presented as percentages across included studies

9. In-person evaluations of the accuracy of dermoscopy added to visual inspection grouped by pathway categorisation for detecting invasive melanoma or atypical intraepidermal melanocytic variants

11. Comparison of the accuracy of visual inspection with visual inspection (VI) + dermoscopy for detection of invasive melanoma or atypical intraepidermal melanocytic variants from in-person studies

Bottom lines for some reviews
Topics covered: melanoma – visual inspection

- Lots of studies: (49 papers, 34,351 lesions, 2499 cases providing 134 datasets
- Standard practice but will miss melanoma if used alone
- In-person better than images
- Evidence generally flawed and poorly reported
- Algorithms don’t improve accuracy, but not enough evidence in key settings to dismiss
- Further prospective evaluation of algorithms according to prior testing and diagnostic difficulty
Melanoma – dermoscopy and RCM

- **Dermoscopy** - adds benefit esp. in referred people and in experienced hands. Data in primary care lacking – needs testing with various algorithms

- **Reflectance confocal microscopy** not much data, but may be useful for lesions difficult to diagnose using inspection and dermoscopy alone for diagnosing cutaneous melanoma in adults
Melanoma: smartphone apps

- Easy access to public and immediate risk assessment
- Evidence limited so far (two cohorts, 5 apps)
- Up to 15% unevaluable
- Worrying risk of missing melanoma (sensitivity ranged from 7% to 73%)
Keratinocyte skin cancer - basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC)

- **Dermoscopy** - maybe useful in secondary care as an adjunct in mixed lesions alone or in combination, for diagnosing BCC in adults. No clear evidence on benefit of algorithms. Nil on cSCC

- **Reflectance confocal microscopy** - insufficient evidence

- **Exfoliative cytology** - unclear utility for diagnosis but good for confirming strongly suspected BCC clinical diagnoses
Melanoma, BCC and cSCC

- **Teledermatology:** 22 studies generally poorly reported. Likely to improve triage from primary to secondary care for possibly malignant lesions that may require excision but evidence base not strong.

- **Computer-assisted diagnosis:** sensitivity looks good eg to reassure specialists they have not missed melanoma, but evidence to translate to clinical practice limited. Unclear which system is best and unclear if helpful for keratinocyte cancers or in primary care setting.
Melanoma, BCC and cSCC

- **High-frequency ultrasound**: insufficient evidence

- **Optical coherence tomography** for diagnosing skin cancer in adults – maybe useful for difficult to diagnose BCC but insufficient evidence to date
What does it all mean?

- So much unclear due to flawed designs and poor reporting especially external validity (applicability)

- Perhaps only clear message is on potential benefit of dermoscopy

- Use of algorithms uncertain

- Critical to refer to the population, setting and clinical pathway
People with skin lesions
Present directly to generalist clinician (e.g. GP)

Generalist clinician
- History, examination, possible clinical/dermoscopic photographs
- Teledermatology consultation, if available

Clinical suspicion:

- Melanoma
- cSCC
  - Urgent referral (2WW in UK)

- High risk BCC
  - Atypical lesions
  - Non-urgent referral

- Low risk BCC

- Benign

Treated by GP
- Non-surgical therapy according to national/international guidelines

Specialist clinic
- History, examination, possible clinical/dermoscopic photographs

Urgent action
- melanoma
- cSCC
- high risk BCC
  - Incisional biopsy/ excisional biopsy (2mm margin) excision according to national/international guidelines e.g. with 1cm clearance

Less urgent action
- low risk BCC
- lentigo maligna
  - Possible biopsy/ excision according to national/international guidelines

Surveillance
- severe dysplasia
- high risk groups
  - Possible biopsy

No action/Discharge
- Patient reassurance
- Advice on cosmetic removal

2WW - two week wait; GP - general practitioner; cSCC - cutaneous squamous cell cancer; BCC - basal cell cancer
Hywel’s pick of research priorities

- Harmonise **pathways and outcomes** to develop a common international language
- Abide by some **basic standards** for design and conduct of derm DTA (STARD and QUADAS2) – work with methods people
- Evaluate **dermoscopy in primary care** plus whether algorithms help or confuse
- Telederm for **primary care triage**
- Update **smartphone apps review** as field progressing rapidly
Hywel and his Welsh three-legged EBM milking stool
What did I learn?

- **Utility** is more important than just sensitivity and specificity
- Trending things like AI image analysis still not that good so far
- General standard of DTA research in skin cancer is lousy - “Technology good, evaluation poor”
- Mainly due to lack of consideration of classical DTA biases and matching research question to the clinical situation rather than to the technology
- **Respect** to fantastic team although nearly killed us
Thank you to:

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