Diagnostic test accuracy for skin cancer project:

Implications for practice and research

Hywel Williams on behalf of NIHR HTA Skin Cancer DTA team

Universities of Nottingham and Birmingham

January 8th Paris

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

Funded by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group and Cochrane Programme Grant funding. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or Department of Health.

Cochrane Special Collections

Diagnosing skin cancer

6 December 2018

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 tissue. 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)

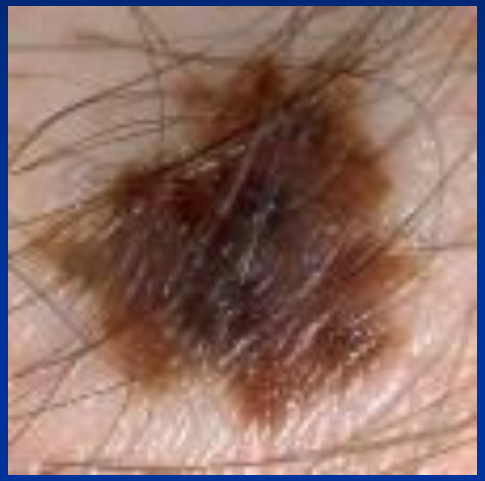
Keratinocyte skin cancer - basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC)

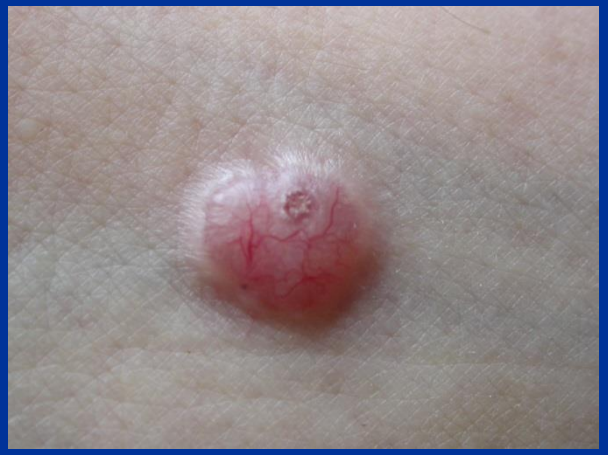
- Visual inspection and dermoscopy, alone or in combination, for diagnosing keratinocyte skin cancers in adults
- Reflectance confocal microscopy for diagnosing keratinocyte skin cancers in adults
- Exfoliative cytology for diagnosing basal cell carcinoma and other skin cancers in adults

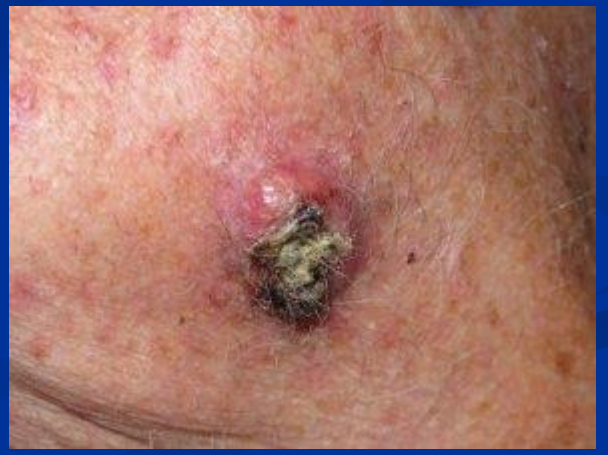
Topics Covered: diagnosis of skin cancers including melanoma, BCC and cSCC

- 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

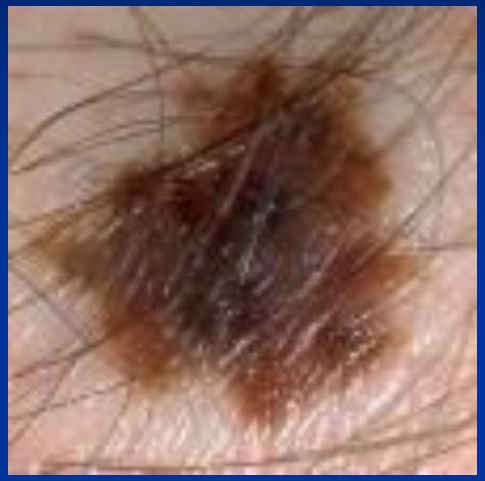
Sensitivity and specificity

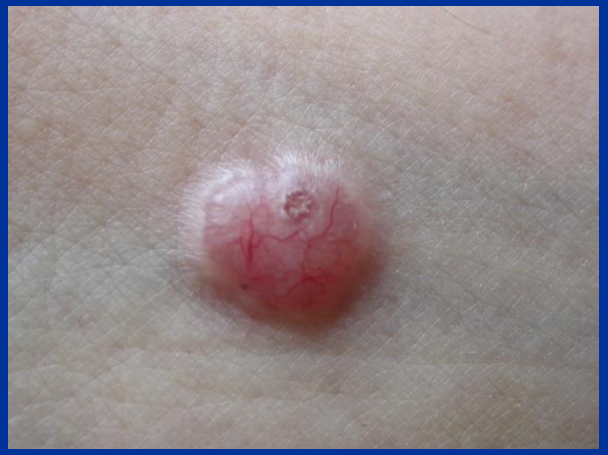


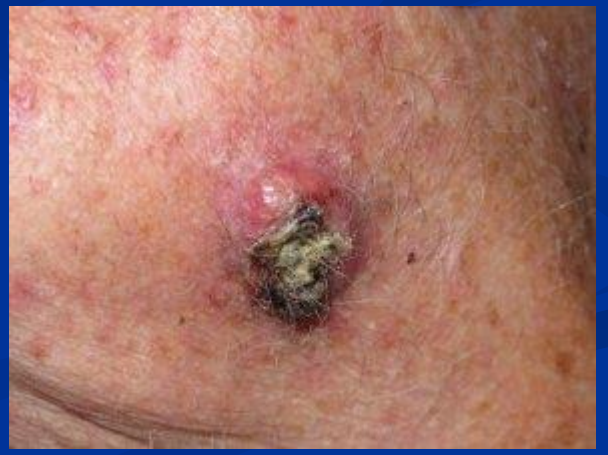




Sensitivity & specificity: trade-off requirement will vary







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

How did we do it? – dermoscopy example

- 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

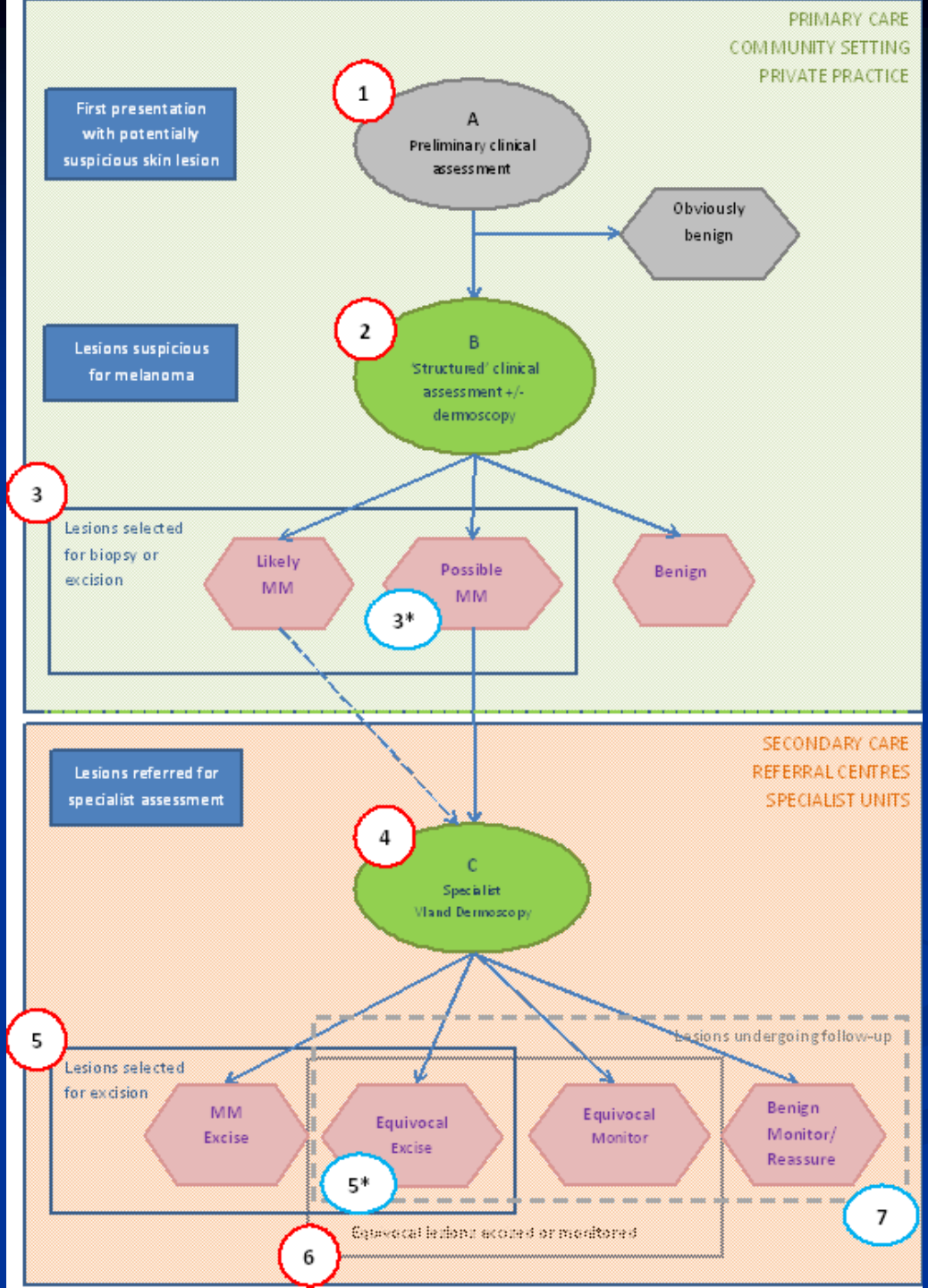
- Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on QUADAS-2). We contacted authors of included studies where information related to the target condition or diagnostic threshold were missing. training.

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


PRIMARY CARE
COMMUNITY SETTING
PRIVATE PRACTICE
First presentation with potentially suspicious skin lesion
1
A
Preliminary clinical assessment
Obviously benign
Lesions suspicious for melanoma
2
B
'Structured' clinical assessment +/- dermoscopy
3
Lesions selected for biopsy or excision
Likely MM
Possible MM
3*
Benign
SECONDARY CARE
REFERRAL CENTRES
SPECIALIST UNITS
Lesions referred for specialist assessment
4
C
Specialist
Wand Dermoscopy
5
Lesions selected for excision
MM Excise
Equivocal Excise
5*
Equivocal Monitor
Benign Monitor/ Reassure
Lesions undergoing follow-up
7
6

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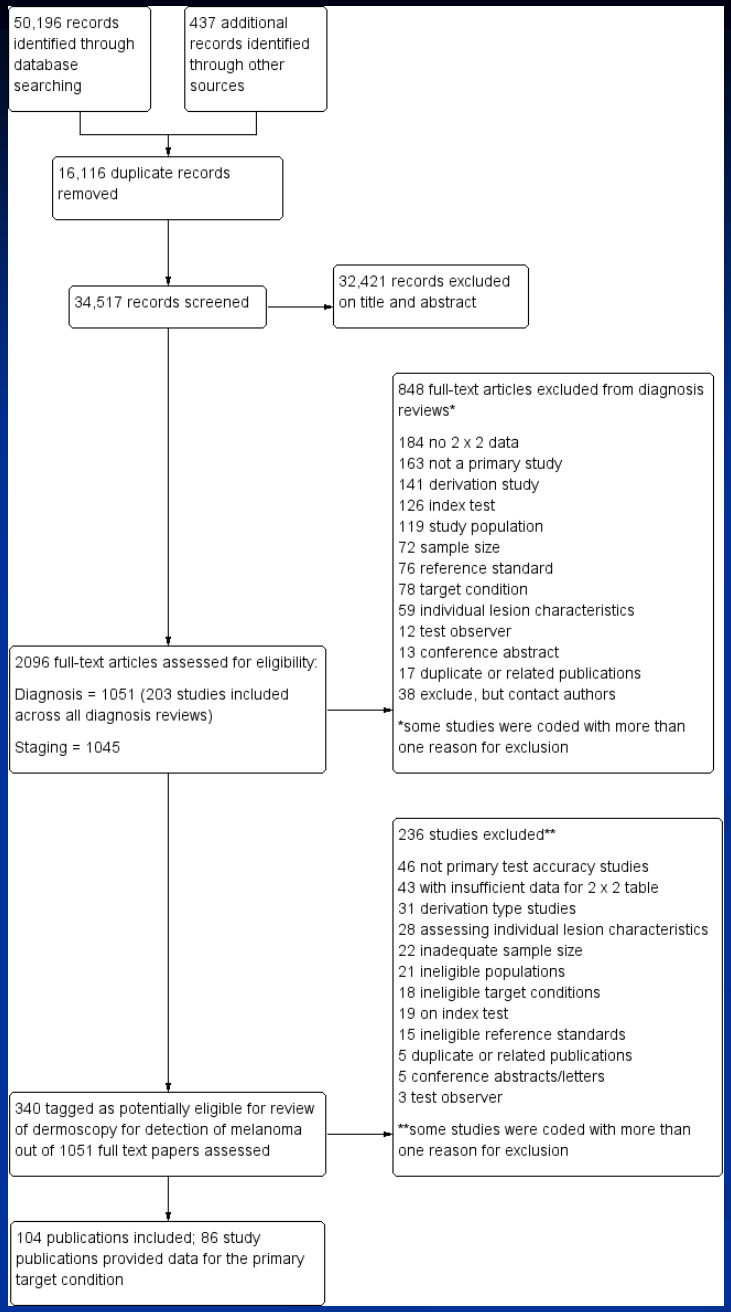
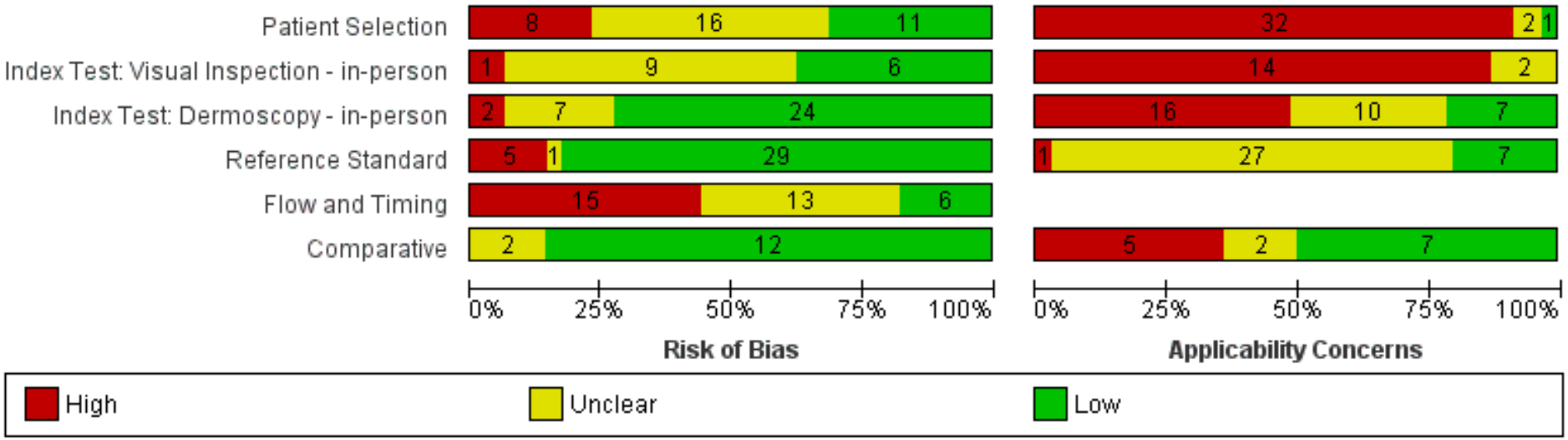


4. PRISMA flow diagram.

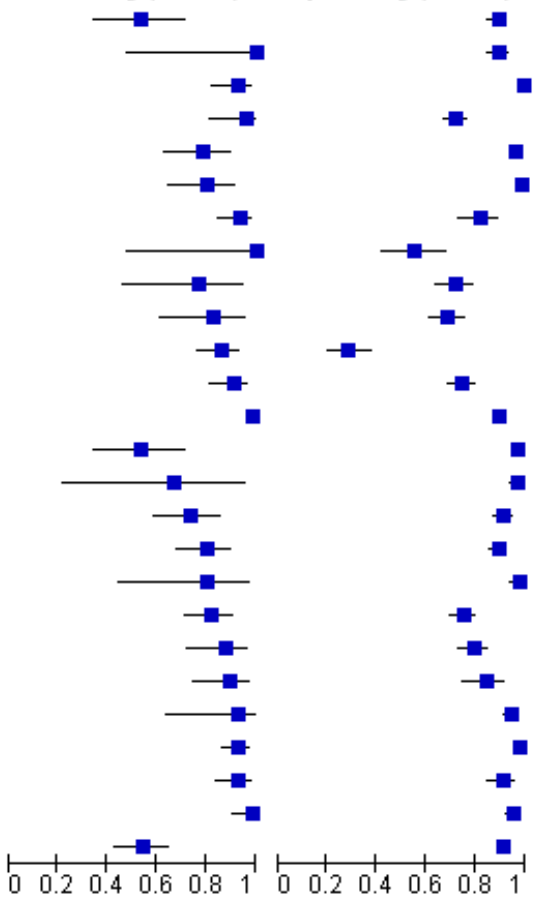
Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, Wong KY, Aldridge RB, Abbott R, Fawzy M, Bayliss SE, Grainge MJ, Takwoingi Y, Davenport C, Godfrey K, Walter FM, Williams HC. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database of Systematic Reviews 2018, 12. Art. No.: CD011902. DOI: http://dx.doi.org/10.1002/14651858.CD011902.pub2



5. Risk of bias and applicability concerns graph for in-person evaluations: review authors' judgements about each domain presented as percentages across included studies

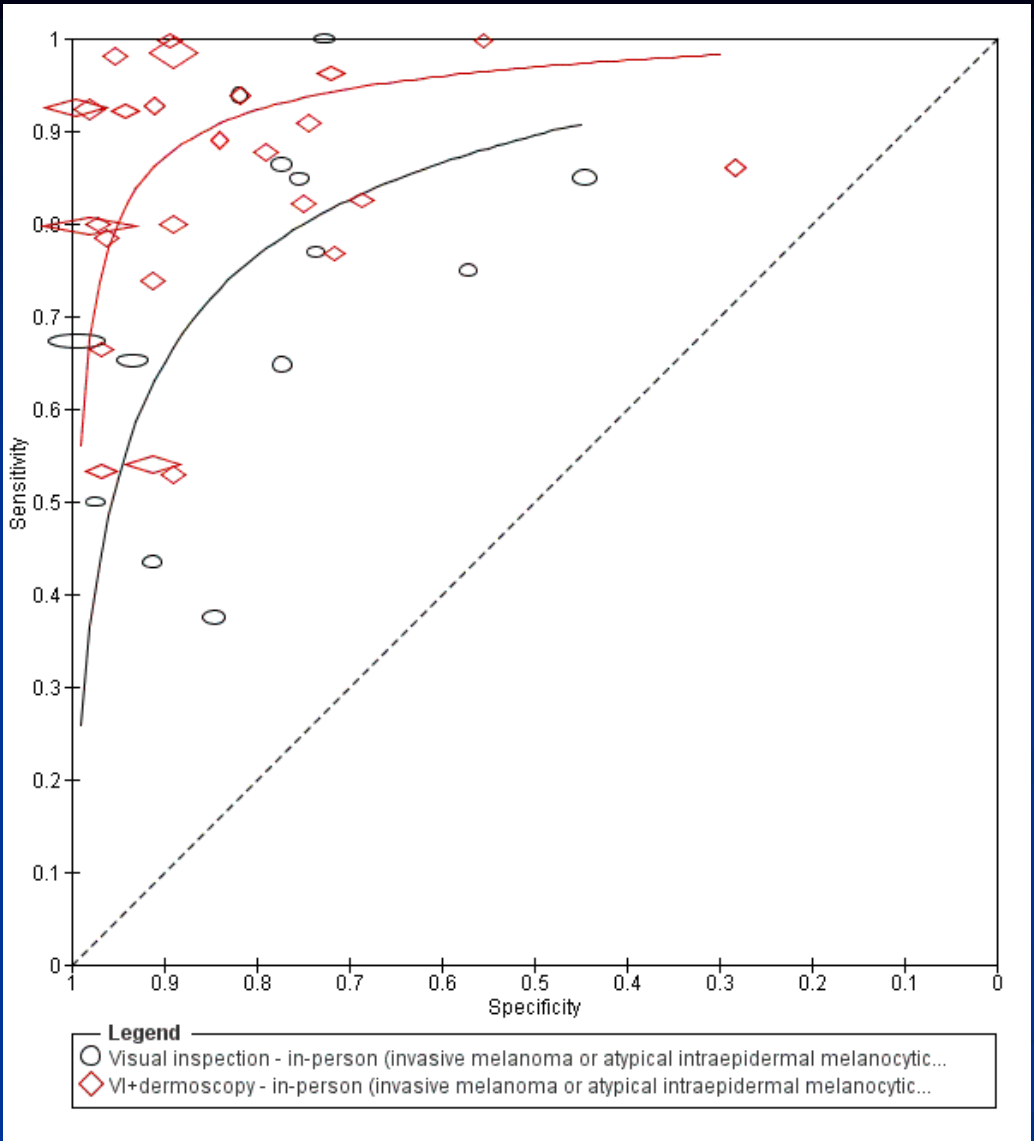
Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, Wong KY, Aldridge RB, Abbott R, Fawzy M, Bayliss SE, Grainge MJ, Takwoingi Y, Davenport C, Godfrey K, Walter FM, Williams HC. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database of Systematic Reviews 2018, 12. Art. No.: CD011902. DOI: http://dx.doi.org/10.1002/14651858.CD011902.pub2

Study	TP	FP	FN	TN	Pathway	Sensitivity (95% CI)	Specificity (95% CI)
Menzies 2009	17	33	15	266	2-c	0.53 [0.35, 0.71]	0.89 [0.85, 0.92]
Grimaldi 2009	5	24	0	206	2-c	1.00 [0.48, 1.00]	0.90 [0.85, 0.93]
Stanganelli 2000	51	9	4	3308	4-c	0.93 [0.82, 0.98]	1.00 [0.99, 1.00]
Dreiseitl 2009	26	121	1	310	4-c	0.96 [0.81, 1.00]	0.72 [0.67, 0.76]
Bauer 2000	33	10	9	263	4-u	0.79 [0.63, 0.90]	0.96 [0.93, 0.98]
Haenssle 2010a (FV)	32	146	8	8263	4-u	0.80 [0.64, 0.91]	0.98 [0.98, 0.99]
Soyer 1995	61	17	4	77	5*-c	0.94 [0.85, 0.98]	0.82 [0.73, 0.89]
Carli 1994	5	28	0	35	5*-c	1.00 [0.48, 1.00]	0.56 [0.42, 0.68]
Bono 2002b	10	42	3	106	5-c	0.77 [0.46, 0.95]	0.72 [0.64, 0.79]
Bono 2006	19	57	4	126	5-c	0.83 [0.61, 0.95]	0.69 [0.62, 0.75]
Guitera 2009a (Modena)	68	83	11	33	5-c	0.86 [0.76, 0.93]	0.28 [0.20, 0.38]
Bono 2002a	60	63	6	184	5-c	0.91 [0.81, 0.97]	0.74 [0.69, 0.80]
Duff 2001	577	193	9	1593	5-c	0.98 [0.97, 0.99]	0.89 [0.88, 0.91]
Feldmann 1998	16	14	14	456	5-u	0.53 [0.34, 0.72]	0.97 [0.95, 0.98]
Morales Callaghan 2008	4	6	2	188	5-u	0.67 [0.22, 0.96]	0.97 [0.93, 0.99]
Ahnlide 2016	34	23	12	240	5-u	0.74 [0.59, 0.86]	0.91 [0.87, 0.94]
Benelli 1999	48	37	12	304	5-u	0.80 [0.68, 0.89]	0.89 [0.85, 0.92]
Durdu 2011	8	5	2	185	5-u	0.80 [0.44, 0.97]	0.97 [0.94, 0.99]
Kittler 1999	60	71	13	212	5-u	0.82 [0.71, 0.90]	0.75 [0.69, 0.80]
Cristofolini 1994	29	39	4	148	5-u	0.88 [0.72, 0.97]	0.79 [0.73, 0.85]
Langley 2007	33	14	4	74	5-u	0.89 [0.75, 0.97]	0.84 [0.75, 0.91]
Gokdemir 2011	12	25	1	410	5-u	0.92 [0.64, 1.00]	0.94 [0.92, 0.96]
Broganelli 2005	100	10	8	520	5-u	0.93 [0.86, 0.97]	0.98 [0.97, 0.99]
Nachbar 1994	64	11	5	114	5-u	0.93 [0.84, 0.98]	0.91 [0.85, 0.96]
Carli 2002a	53	9	1	193	5-u	0.98 [0.90, 1.00]	0.96 [0.92, 0.98]
Haenssle 2010b (FU)	47	228	40	2373	7-u	0.54 [0.43, 0.65]	0.91 [0.90, 0.92]



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

Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, Wong KY, Aldridge RB, Abbott R, Fawzy M, Bayliss SE, Grainge MJ, Takwoingi Y, Davenport C, Godfrey K, Walter FM, Williams HC. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database of Systematic Reviews 2018, 12. Art. No.: CD011902. DOI: http://dx.doi.org/10.1002/14651858.CD011902.pub2



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

Dinnes J, Deeks JJ, Chuchu N, Ferrante di Ruffano L, Matin RN, Thomson DR, Wong KY, Aldridge RB, Abbott R, Fawzy M, Bayliss SE, Grainge MJ, Takwoingi Y, Davenport C, Godfrey K, Walter FM, Williams HC. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. Cochrane Database of Systematic Reviews 2018, 12. Art. No.: CD011902. DOI: http://dx.doi.org/10.1002/14651858.CD011902.pub2

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

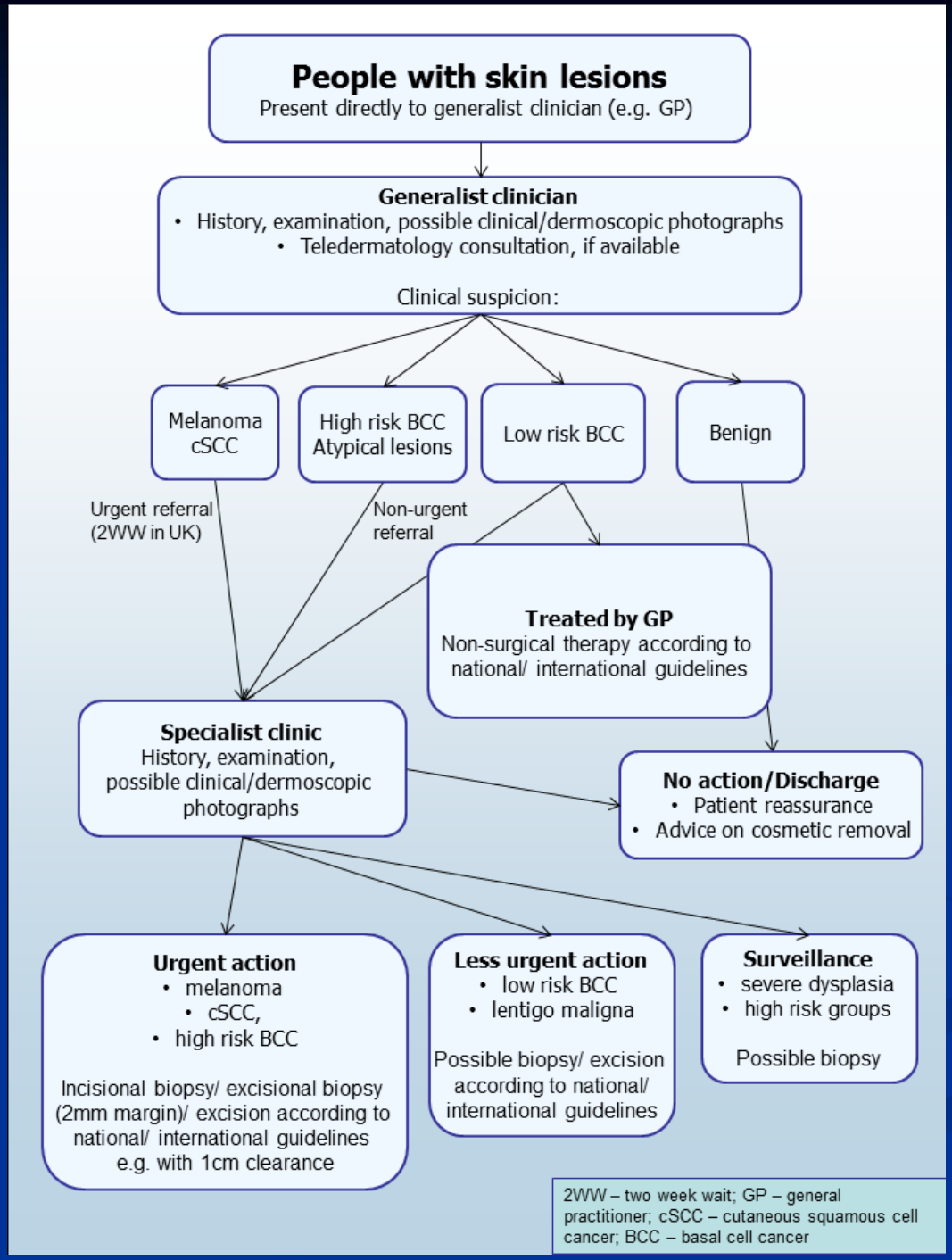
- Teledermatology: 22 studies generally poorly reported. Likely to improve triage from primary to secondary care for possibly malignant lesions that may require excision but evidence base not strong
- Computer-assisted diagnosis: sensitivity looks good eg to reassure specialists they have not missed 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
High risk BCC Atypical lesions
Low risk BCC
Benign
Urgent referral (2WW in UK)
Non-urgent referral
Treated by GP
Non-surgical therapy according to national/ international guidelines
Specialist clinic
History, examination, possible clinical/dermoscopic photographs
No action/Discharge
• Patient reassurance
• Advice on cosmetic removal
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
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

The Evidence

The Practitioner

The Patient

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:

Members of the Cochrane Skin Cancer Diagnostic Test Accuracy Group include:
The full project team (Susan Bayliss, Lavinia Ferrante di Ruffano, Naomi Chuchu, Clare Davenport, Jonathan Deeks, Jac Dinnes, Kathie Godfrey, Rubeta Matin, Colette O'Sullivan, Yemisi Takwoingi, Hywel Williams);
Our 12 clinical reviewers (Rachel Abbott, Ben Aldridge, Oliver Bassett, Sue Ann Chan, Alana Durack, Monica Fawzy, Abha Gulati, Jacqui Moreau, Lopa Patel, Daniel Saleh, David Thompson, Kai Yuen Wong) and two methodologists (Lavinia Ferrante di Ruffano and Louise Johnston), who assisted with full-text screening, data extraction and quality assessment across the entire suite of reviews of diagnosis and staging and skin cancer;
Our expert advisors (Jeff Bamber, Fiona Bath-Hextall; Jonathan Bowling, Seau Tak Cheung, Colin Fleming, Matthew Gardiner, Abhilash Jain, Susan O'Connell , Pat Lawton, John Lear, Mariska Leeflang, Richard Motley, Paul Nathan, Julia Newton-Bishop, Miranda Payne, Rachael Robinson, Simon Rodwell, Julia Schofield, Neil Shroff, Hamid Tehrani, Zoe Traill, Fiona Walter, Angela Webster. Rakesh Patalay).
The Cochrane Skin editorial base esp. Helen and Laura and Liz and Robert Dellavalle and Bob Boyle
All the referees and Cochrane copy editors
Cochrane DTA editorial base for rapid reviewing

Cochrane Special Collections

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6 December 2018

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