prognostic factors. In practice, the predictors of biomarkers will need to be assessed alongside clinical phenotypic and demographic factors.[1]

Biomarkers can potentially help us with the prediction of the cause of a disease, its progression, regression, outcome, diagnosis and, in the case of the scoping review in this issue of the BJD,[2] the results of treatment. However, the sheer volume of the biomarker literature is in stark contrast to the few biomarkers that have established utility in clinical practice,[3] especially in inflammatory disease.

Protagonists of what is possible with the translation of this approach into clinical practice envisage being able to assess a patient alongside their molecular screen with biochemical and genetic predictors that will enable personalized medicine choices to be made for optimal response, most cost-effective treatment pathways and avoiding harms.[4]

In this issue of the BJD, Corbett et al.[2] present a comprehensive scoping review of the biomarker literature aimed at improving outcomes by predicting the effectiveness and safety of treatments for psoriasis. It is broad, including 71 studies and covering 17 different treatments, mostly biological therapies.

A significant failure rate with a treatment modality should lend itself to the biomarker approach. While conventional treatments were included in the scope, the authors found most potential biomarkers predict the response to antitumour necrosis factor therapy, with one marker for response to ustekinumab. However, none were ready for clinical application without further validation. For those working in this field, this scoping review helps signpost the areas for further research.

A good biomarker should be easy to sample and quantify and cost-efficient to process. It should be directly involved in disease pathogenesis. The authors have mapped the biomarkers onto the known pathways of importance for psoriasis including antigen processing and presentation (HLA-C*06:02), T-helper 17 cell differentiation [interleukin (IL)1B] and immune response (IL12B), and regulation of nuclear factor-κB activity (CARD14, IL17RA).[2]

Their critical appraisal of these studies showed that much of the evidence base was of poor quality, with methodological and reporting limitations that excluded many studies. This has led to important recommendations for future research which in turn should ensure more effective biomarker research, going forward.

Those biomarkers to take forward are clearer from the 'catalogue' presented by Corbett et al.[2] To be useful, they will need to demonstrate strong association with the desired outcome and specificity, applying similar predictive testing to those applied to diagnostic tests. The complexity of psoriasis pathogenesis, its multiple pathways and the treatment modalities involved ensure that this will require much more work. Perhaps a less directed hypothesis-free approach, a more recent development, holds promise and could lead to new mechanistic insights. There may also be scope for timely integration of biomarkers into drug development in this rapidly changing therapeutic area.

Anthony D. Ormerod (iD)

University of Aberdeen, Aberdeen, UK
Email: a.d.ormerod@abdn.ac.uk

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References

1 Warren RB, Marsden A, Tomenson B et al. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. *Br J Dermatol* 2019; **180**:1069–76. https://doi.org/10.1111/bjd.16776.
2 Corbett M, Ramessur R, Marshall D et al.; on behalf of the BIO-MAP consortium. Biomarkers of systemic treatment response in people with psoriasis: a scoping review. *Br J Dermatol* 2022; **187**:494–506.
3 Burke HB. Predicting clinical outcomes using molecular biomarkers. *Biomark Cancer* 2016; **8**:89–99. https://doi.org/10.4137/BIC.S33380
4 Reid C, Cordingley L, Warren RB et al. Progress to date in advancing stratified medicine in psoriasis. *Am J Clin Dermatol* 2020; **21**:619–26.

Melanoma overdiagnosis: why it matters and what can be done about it

Linked Article: Whiteman et al. Br J Dermatol 2022; **187**:515–522.

Cancer screening aims to reduce morbidity and mortality through early detection of preclinical disease. These potential benefits must be weighed against potential harms from diagnostic procedures, induced anxiety, false-positive or false-negative results and the detection of 'indolent' cancers, otherwise known as overdiagnosis. The actual benefits and harms from melanoma screening remain contested in the absence of robust evidence from randomized clinical trials.

The analysis by Whiteman and colleagues of a large Australian prospective cohort study is a valuable addition to the evidence base. Using a propensity score-based analysis, they obtained results that may approximately mimic those from a trial of melanoma screening.[1] Participants who had a prior clinical skin examination were 30% more likely have a new diagnosis of melanoma than controls. Those who had a skin biopsy in the first year of follow-up were 50% more likely. The difference in cumulative risk increased over time to a

0·5% absolute risk difference at 5 years (screened 1·94%, unscreened 1·45%). More than 60% of new diagnoses were in situ melanomas. Restricting the primary analysis to invasive melanomas, the difference between screened and unscreened largely disappeared (adjusted hazard ratio 1·05, 95% confidence interval 0·72–1·63). These data strongly suggest substantial melanoma overdiagnosis because of screening, particularly overdiagnosis of melanoma in situ.

Limitations of the study, noted by the authors, would tend to underestimate overdiagnosis. These include use of proxies for screening (prior self-reported skin examination and incident skin biopsy), high background rates of screening (73% of people had prior skin checks), and considerable crossover (23% of those screened 'dropped out' of and 33% of those unscreened 'dropped in' to screening). Longer follow-up will increase certainty on the extent of overdiagnosis, and may also yield insights into potential beneficial impacts from screening on decreasing advanced-stage melanoma and melanoma mortality.

Overdiagnosis occurs when a person is diagnosed with melanoma but they would never have experienced symptoms or harm from that lesion had it been left undetected and untreated.[2,3] It causes harm through the melanoma diagnosis itself,[4] and by leading to unnecessary treatment, tests and other healthcare such as long-term clinical surveillance.[5] Epidemiological data in the USA suggest that despite rapidly increasing rates of early-stage melanoma, the rates of clinically important melanoma may not have changed much over the last 40 years.[2] The increase in melanoma in situ is notable, with rates approximating those of invasive melanoma from 2015. Similar trends can be found in Australia, where a recent population-level analysis estimated that 58% of all melanomas (22% of invasive melanomas) in men, and 54% of melanomas (15% of invasive melanoma) in women were overdiagnosed.[6]

Epidemiological data such as these suggest that routine skin examinations may not be as effective in preventing advanced-stage melanoma and death as was hoped. Further indirect evidence of this is provided by a recent nationwide analysis of Netherlands Cancer Registry data. Researchers found that delays in screening caused by COVID-19 may have had limited impact on the tumour characteristics of primary invasive melanomas, at least in the short term.[7] One approach to increase benefits and decrease harms is to target screening to those at higher risk, as suggested by the US Preventative Services Task Force recommendations for research. Given the risk of melanoma overdiagnosis, it may be most helpful to target screening to those at highest risk of developing advanced-stage melanoma or of dying from melanoma.[8]

Information to develop risk tools that identify such people may be provided by cancer registry data that include all melanomas that progress to stage IV disease, regardless of stage at first diagnosis.[9] In addition, where the initial diagnosis was early stage disease (which later progressed), detailed characterization of how these individuals (e.g. immune system) and their tumours (e.g. molecular and genetic markers) differ from the majority of people diagnosed with melanoma in situ or localized invasive melanoma may help to distinguish high-risk lesions (where surveillance, investigations and treatment may be intensified) from potentially indolent ones (where de-intensification may be possible). Until then, melanoma overdiagnosis is largely identifiable only at a population level, and requires population-level interventions for its prevention.[6] Such efforts are urgently needed to minimize harms from early melanoma detection, and ensure the delivery of sustainable, high-value healthcare.[10]

Katy J.L. Bell (iD)[1] and Tamar Nijsten (iD)[2]

[1]Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney, Edward Ford Building (A27), Camperdown, Sydney, NSW, 2006, Australia [2]Department of Dermatology, Erasmus MC Cancer Institute, Doctor Molewaterplein 40, 3015, GD, Rotterdam, the Netherlands Email: katy.bell@sydney.edu.au

References

1 Whiteman DC, Olsen CM, MacGregor S et al. The effect of screening on melanoma incidence and biopsy rates. Br J Dermatol 2022; **187**:515–22.

2 Welch HG, Mazer BL, Adamson AS. The rapid rise in cutaneous melanoma diagnoses. N Engl J Med 2021; **384**: 72–9.

3 Semsarian CR, Ma T, Nickel B et al. Do we need to rethink the diagnoses melanoma in situ and severely dysplastic naevus? Br J Dermatol 2022; **186**:1030–2.

4 Bell KJL, Mehta Y, Turner RM et al. Fear of new or recurrent melanoma after treatment for localised melanoma. Psychooncology 2017; **26**:1784–91.

5 Ackermann DM, Dieng M, Medcalf E et al. Assessing the Potential for Patient-led Surveillance After Treatment of Localized Melanoma (MEL-SELF): a pilot randomized clinical trial. JAMA Dermatol 2022; **158**: 33–42.

6 Glasziou PP, Jones MA, Pathirana T et al. Estimating the magnitude of cancer overdiagnosis in Australia. Med J Aust 2020; **212**:163–8.

7 Sangers TE, Wakkee M, Kramer-Noels EC et al. Limited impact of COVID-19-related diagnostic delay on cutaneous melanoma and squamous cell carcinoma tumour characteristics: a nationwide pathology registry analysis. Br J Dermatol 2022; **187**:196–202.

8 Welch HG, Brawley OW. Scrutiny-dependent cancer and self-fulfilling risk factors. Ann Intern Med 2018; **168**: 143–4.

9 Zhou C, Louwman M, Wakkee M et al. Primary melanoma characteristics of metastatic disease: a nationwide cancer registry study. Cancers 2021; **13**: 4431.

10 Barratt A, McGain F. Overdiagnosis is increasing the carbon footprint of healthcare. BMJ 2021; **375**: n2407.