Management of cutaneous melanoma in Australia: a narrative review

Prachi Bhave[1,2], Jessica Wong[3], Aideen McInerney-Leo[4,5], Anne E Cust[5,6], Craig Lawn[6,7], Monika Janda[8], Victoria J Mar[2,9]

Summary

- Australia has one of the highest rates of cutaneous melanoma in the world. In the absence of a formal melanoma screening program, most screening in Australia is currently opportunistic and not tailored to an individual patient's risk.
- Several melanoma risk prediction tools are available online, but most have not been externally validated, limiting their clinical uptake.
- Advanced diagnostic technologies are becoming increasingly available, some of which are augmented with machine learning; however, their accuracy and role in clinical practice remains to be determined.
- Surgery remains the foundation for treatment of primary melanoma and is based on complete resection of the primary lesion with appropriate clear margins. Sentinel lymph node biopsy, performed in certain patients with high risk pathological features in their primary melanoma, is the gold standard for determining regional lymph node involvement and provides prognostic information that can guide the use of adjuvant therapy.
- In the past decade, the median survival of patients with advanced melanoma has increased from the order of a few months to potentially over five years due to the availability of immune checkpoint inhibitors and *BRAF*/MEK inhibiting targeted therapy. These treatments are also available in an adjuvant setting, halving the risk of recurrence after surgical resection of the primary tumour or following regional nodal resection.
- A large community of melanoma survivors and their family, friends and carers are now actively involved in research efforts and play a central role in improving models of care and ensuring a holistic approach to patient management.

Australia has one of the highest incidences of cutaneous melanoma in the world.[1] Indeed, melanoma is so common that it is estimated to be the third most diagnosed cancer in Australia in 2022 and is the most common cancer in people aged 20–39 years.[1] The management of melanoma continues to evolve, with significant advances being made over historical approaches, resulting in improved patient outcomes. This review provides a concise overview of the screening, diagnosis and management of melanoma in Australia.

Methods

We conducted a literature search on the MEDLINE and PubMed electronic databases for articles published from 2000 to 2022 to include updated data on the management of melanoma. Articles in English and studies involving humans only were included. The search included combinations of the keywords "melanoma", "cutaneous melanoma", "metastatic melanoma", "risk assessment", "risk models", "risk prediction", "risk stratification", "polygenic risk", "genome wide association studies", "diagnosis", "imaging", "biopsy", "surgery", "resection", "excision", "immunotherapy", "checkpoint inhibitors", "targeted therapy", "adjuvant therapy" and "neoadjuvant therapy". Specialist society publications and guidelines were also reviewed, including those from Cancer Council Australia, the American Society of Clinical Oncology and the European Society for Medical Oncology. There were no exclusions on article type, and abstracts, review articles, letters and editorials were considered.

Advances in risk assessment

There is currently insufficient evidence to assess the impact of skin cancer screening on melanoma mortality,[2] with a recent Australian study finding that skin screening increases the risk of biopsy and melanoma in situ without increasing the detection rate of invasive melanoma compared with unscreened individuals.[3] However, most clinical practice guidelines recommend regular skin checks and prevention advice for people at high risk of melanoma or other skin cancers.[4-6] A targeted approach to screening high risk individuals may be cost-effective,[7,8] but further evidence is needed.

To identify individuals at high risk, clinicians have historically relied on phenotypic features such as naevi and pigmentation (skin, hair and eye colour) as well as personal and family history of skin cancer. Epidemiology studies on twins have demonstrated that about 58% of melanoma incidence is attributable to genetic variation.[9] Although 10% of individuals with melanoma will have an affected first degree relative,[10] only 10% of those cases will have a strong family history (ie, three or more cases related in the first or second degree).[11,12] Therefore, familial melanoma accounts for a relatively small portion of melanoma heritability. Familial risk in some families can be explained by the presence of high penetrance variants in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene, by clustering of low penetrance variants across multiple genes or by behavioural factors.[13,14] Large genome-wide association studies have evaluated the frequency of common genetic variants among people with and without melanoma. The most recent meta-analysis of these studies revealed 68 independent genetic variations (single nucleotide polymorphism) in 54 loci as being associated with modest melanoma risk.[15] As would be expected from the clinical risk factors above, some of the genes associated with these single nucleotide polymorphisms are implicated in pigmentation or naevus susceptibility.[15]

More recently, risk prediction models have been developed to improve the accuracy of risk stratification,[16] and several Australian melanoma risk tools are freely available online and can be used to guide informed discussions between clinicians and patients about prevention, screening and treatment.[17-19] It is important to note, however, that most risk prediction

[1] Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC. [2] Alfred Hospital, Melbourne, VIC. [3] Princess Alexandra Hospital, Brisbane, QLD. [4] Dermatology Research Centre, University of Queensland Diamantina Institute for Cancer Immunology and Metabolic Medicine, Brisbane, QLD. [5] Australian Centre of Excellence in Melanoma Imaging, Brisbane, QLD. [6] Melanoma Institute Australia, Sydney, NSW. [7] Centre of Excellence in Melanoma Imaging, Brisbane, QLD. [8] Centre for Health Services Research, University of Queensland, Brisbane, QLD. [9] Monash University, Melbourne, VIC. victoria.mar@monash.edu • doi: 10.5694/mja2.51910

models rely on self-reporting and only a few of these models have been externally validated. Of those that have, acceptable discriminatory ability has been shown, thus enabling risk stratification and tailored prevention in clinical practice.[20-23] However, most models demonstrated poor calibration, suggesting that the methods for estimating absolute risk need careful consideration to ensure accurate prediction of the number of cases in the population,[22] which is relevant for population screening programs.[20,21,23] By combining the odds ratios and frequencies of genome-wide association studies of single nucleotide polymorphisms, it is possible to generate an individual's polygenic risk score. Studies have shown that melanoma polygenic risk scores have similar risk prediction performance to models based on traditional risk factors,[24] and, when combined, they result in a modest incremental improvement in discrimination, sensitivity and specificity.[25] Further research is needed to guide the integration of sociodemographic, clinical and genomic risk factors into risk prediction models and their implementation in practice.

Advances in diagnostic technology

In the absence of evidence to support implementation of a formal melanoma screening program, screening is currently opportunistic and not necessarily targeted towards individuals at highest risk. The current screening procedure relies on a full skin examination by a clinician. Diagnostic accuracy varies between clinicians according to experience and training.[26] In addition, high discordance between pathologists in identifying benign naevi versus melanoma has also been observed.[27,28] Variable accuracy is one factor contributing to the high burden of benign "just in case" biopsies as well as missed opportunities for early detection.[8,29] Rates of melanoma in situ diagnosis are increasing significantly without a corresponding reduction in mortality.[30] Therefore, there is increasing concern about overdiagnosis (finding lesions that would not cause harm) and the impact of this on patient wellbeing and health system costs as well as the phenomenon of "diagnostic drift" (the tendency to upstage borderline or precursor lesions as malignant over time).[31,32] Emerging software applications powered by machine learning have the potential to improve the inter- and intra-observer variability in the diagnosis of skin lesions using images from professional total body photography through to "selfies" from modern smartphones.[33]

There is observational evidence to support the use of total-body photography for surveillance of high risk individuals to improve both early detection and reduce unnecessary biopsies.[8,34,35] However, imaging is costly, not widely or consistently used, and not currently covered by Medicare. An Australian randomised control trial is currently underway to evaluate the clinical impact and cost effectiveness of using melanoma surveillance photography for those at high risk of melanoma, from a health system perspective, run through melanoma and skin cancer trials (ClinicalTrials.gov, NCT04385732).

Although advanced diagnostic imaging technology is currently being implemented, there is a relative lack of evidence supporting its clinical efficacy and cost-effectiveness.[36] For example, machine learning algorithms are integrated into imaging systems that can detect change in individual lesions and provide risk assessments for malignancy. Despite impressive data on algorithm performance compared with dermatologists in experimental settings, there are several unknowns about machine learning performance in the real world.[37-39] Studies have shown, for example, that machine learning algorithms are most beneficial to improve accuracy of diagnosis for inexperienced clinicians but less helpful for experienced clinicians.[39] Inaccurate machine learning algorithms may therefore inappropriately influence clinicians and must be used with caution.[39] Other unanswered questions include whether machine learning algorithms developed overseas remain accurate and robust in the Australian population, where machine learning fits into the diagnostic paradigm (eg, as a triage or second opinion system), patient trust in the technology, and how machine learning will affect doctor–patient interactions.[39]

An increasing number of consumer smartphone applications (apps) are commercially available for melanoma prevention and early detection. A 2019 review of major smartphone app stores found 66 apps available for melanoma prevention and early detection.[40] Consumer apps mostly promoted skin self-examination and early detection behaviours, and others provided telehealth and machine learning diagnostic capabilities and prevention education. Very few apps had been evaluated in randomised trials, and it is uncertain whether they improve patient outcomes compared with current best practice.[41] Favourable results have also been found for consumer-led mobile teledermoscopy apps that link patients with a doctor.[42] However, when providing risk assessments or diagnostic advice based on machine learning algorithms (without clinician input), there are concerns regarding reliability due to a lack of quality standards or regulatory oversight. Over time, technological advancements are expected to improve machine learning algorithms within apps but these will require clinical trials to assess their effectiveness and limitations in real-world settings.

It is critical for end-users to understand how algorithms are trained.[43] Issues of generalisability and transparency are particularly important, including the accuracy of machine learning in all populations, skin types and tumour subsites (scalp, nails), and whether the machine learning output is explainable.[44] A significant challenge is to determine whether the use of machine learning will further compound current rates of overdiagnosis. These issues require further research before such technology can be recommended for routine clinical use.

Advances in management

A multidisciplinary approach is central to ensuring appropriate care. Correct pathological diagnosis and accurate staging are imperative, as they dictate the treatment approach.

Surgical approach

Excisional biopsy with a 2 mm margin is the most reliable method to accurately diagnose and guide the management of suspicious skin lesions.[45,46] Incisional biopsy carries the risk of an incomplete diagnosis but can be appropriate in selected patients depending on the site and size of the lesion (eg, the face or acral regions).

Following diagnosis, wide local excision is curative for most cases.[45] The recommended radial excision margins are 5 mm for melanoma in situ, 1 cm for T1 (≤ 1.0 mm thickness), 1–2 cm for T2 (> 1.0–2.0 mm), and 2 cm margins for T3 and T4 (> 2.0 mm) melanoma.[45,46] Recent availability of adjuvant systemic therapy for resected disease highlights the need for adequate surgical staging.[45]

For a subset of people with invasive melanoma, sentinel lymph node biopsy (SLNB) is the gold standard for regional lymph

node assessment and should be performed at the time of the definitive primary melanoma wide local excision.[47,48] SLNB is generally recommended for people with melanoma that is >1 mm thick, or 0.8–1 mm thick with adverse features such as ulceration, who clinically do not have lymphadenopathy.[49] SLNB provides accurate staging and prognostic information[49,50] and should be performed at centres with radiological and surgical expertise to reduce false negative and false positive rates.[49] Tumour thickness, ulceration and the presence of melanoma in the sentinel lymph node are the most important prognostic factors for patient survival.[47] Importantly, SLNB involvement and/or the presence of satellites upstages disease to stage III. Currently, patients with resected stage IIIB/C/D[51] or resected stage IV melanoma can access adjuvant therapy including immune checkpoint inhibitors (ICIs) and targeted therapy. Thus, with the advent of adjuvant therapy, SLNB is no longer a purely prognostic tool but also aids in the therapeutic management of patients with high risk primary disease.

Until recently, proceeding to completion lymph node dissection (CLND) was recommended as standard of care for patients found to have a positive SLNB. However, two trials that randomly assigned patients with a positive SLNB to either observation with ultrasound surveillance or immediate CLND found no survival benefit with CLND.[47,49] Therefore, the default for patients with a positive SLNB is now surveillance with clinical examination and nodal basin ultrasound, with CLND reserved for clinically apparent or imaging-detected regional disease or for patients who choose to have the procedure after counselling.[47-50] The management of in-transit or distant metastases should be discussed in a multidisciplinary setting.

Systemic therapy: resectable disease

Adjuvant therapy aims to treat residual micrometastatic disease after histologically complete resection, thus decreasing the chance of recurrence and in turn improving survival.[52] The first trial to explore the use of adjuvant ICIs compared four doses of ipilimumab with placebo in patients with completely resected stage III melanoma. Although a significant improvement in recurrence-free survival and overall survival was demonstrated, 45% of patients developed severe adverse events.[53] Following this, two clinical trials individually explored nivolumab and pembrolizumab as adjuvant monotherapy, administered for one year after surgery.[54,55] Both trials reported similar results, with a halving of the risk of melanoma recurrence after surgery compared with observation and less toxicity compared with ipilimumab, and, thus, both nivolumab and pembrolizumab are available on the Pharmaceutical Benefits Scheme (PBS) as adjuvant therapy. Importantly, both trials are yet to demonstrate whether this decrease in recurrence rate translates to improved overall survival. Adjuvant B-Raf proto-oncogene (*BRAF*)/MEK inhibition with dabrafenib/trametinib combination has also been shown to halve the risk of melanoma recurrence, providing an alternative to adjuvant ICIs in patients with *BRAF* V600 mutant disease.[56] This trial has shown a trend towards improved overall survival, although data are not yet mature.[56]

Systemic therapy: unresectable disease

The prognosis of patients with advanced melanoma has significantly improved over the past decade with the advent of novel therapies, including ICIs and *BRAF*/MEK inhibiting targeted therapy, taking patient survival from the order of months to potentially many years.[57]

Immunotherapy

Anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint inhibitor: ipilimumab. Ipilimumab was the first ICI to demonstrate improved survival of patients with advanced melanoma. Several trials have compared ipilimumab to chemotherapy, vaccine therapy or other historical agents in both treatment-naïve patients and in those who had received prior therapy.[58-60] Ipilimumab was found to improve survival by several months over the alternatives. Importantly, survival rates plateaued with long term follow-up, and, thus, ipilimumab was the first agent to demonstrate that ICIs had the potential of inducing durable disease control.

Anti-programmed cell death 1 (PD-1) immune checkpoint inhibitors: nivolumab and pembrolizumab. Several large clinical trials have demonstrated that both nivolumab and pembrolizumab improve survival over ipilimumab, and these agents are therefore considered standard of care and are commonly used in clinical practice, either as monotherapy or in combination with ipilimumab.[61,62] Patients treated with anti-PD-1 monotherapy have a five-year overall survival rate of about 44%, with less toxicity than ipilimumab.[61,62]

Anti-CTLA-4 and anti-PD-1 combination therapy. Anti-CLTA-4/anti-PD-1 combination therapy was studied in a three-arm trial that randomly assigned patients with previously untreated advanced melanoma to either ipilimumab/nivolumab, nivolumab or ipilimumab. The overall survival at 7.5 years was 48%, 42% and 22% for ipilimumab/nivolumab, nivolumab and ipilimumab respectively, demonstrating that both ipilimumab/nivolumab and nivolumab monotherapy were superior to ipilimumab alone.[62-64] Although the trial was not powered to compare the two nivolumab arms, an exploratory analysis did demonstrate improved survival outcomes with combination therapy. Combination ICI significantly increases the rates of immune-related adverse events compared with anti-PD-1 monotherapy; therefore, the decision to treat with either of these options is made after careful assessment of an individual's risks versus benefits.[62-64]

BRAF and MEK inhibitor targeted therapy

Patients harbouring a *BRAF* V600 mutation are eligible for treatment with oral agents targeting the *BRAF* and *MEK* genes. *BRAF* polymerase chain reaction sequencing is typically performed on tissue following confirmation of advanced (stage III+) disease. *BRAF*/MEK inhibitors classically display a rapid onset of action. In patients with previously untreated advanced melanoma, combination therapy leads to five-year overall survival rates of about 34%, significantly greater than single agent *BRAF* or MEK inhibition.[65] Thus, these agents are rarely administered individually, and current options available in Australia include dabrafenib/trametinib, vemurafenib/cobimetinib and encorafenib/binimetinib. These agents have a unique toxicity profile, including drug fevers, gastrointestinal upset, and skin reactions. Overall, the data supporting all three combination options are similar in terms of efficacy, and, therefore, decisions on which option to prescribe are often based on factors such as toxicity profile and pill burden.[66,67]

Treatment sequencing

Recent data have demonstrated that overall survival is improved in patients initially treated with ICIs rather than targeted therapy, and thus patients with treatment-naïve *BRAF* mutant disease are generally recommended to receive first line immunotherapy.[68,69]

Novel therapies and approaches

With the extraordinary advances described above, the treatment landscape of melanoma continues to be a topic of much interest, with novel therapies and approaches being explored in several clinical trials. Here, we summarise a few of these.

A recent trial demonstrated an improvement in recurrence-free survival with the use of adjuvant pembrolizumab in patients with high risk stage II disease. Although pembrolizumab is not yet available on the PBS for this indication, this trial provides promising early evidence that adjuvant ICIs may be beneficial in earlier stage disease.[70] The use of adjuvant targeted therapy in earlier stage melanoma is also being explored. The Columbus-AD trial is currently recruiting patients across multiple Australian sites, investigating the benefit of adjuvant encorafenib and binimetinib in high risk stage II melanoma with a *BRAF* mutation (ClinicalTrials.gov, NCT05270044).

CTLA-4 and PD-1 represent only two of many potential immunotherapy targets. Recently, the combination of relatlimab (a lymphocyte activation gene-3 [LAG-3] inhibitor) and nivolumab was shown to improve progression-free survival compared with nivolumab alone.[71] Furthermore, this combination resulted in fewer high grade immune-related adverse events compared with previous studies of combination ipilimumab and nivolumab. Although overall survival results are not yet mature, this represents an exciting potential new treatment option in the armamentarium against advanced melanoma.

Neoadjuvant therapy represents a new approach to melanoma management and involves administering systemic therapy for a short duration before surgery in patients with resectable stage III disease. Several advantages are provided by neoadjuvant over adjuvant therapy, including assessment of treatment response, allowing treatment alteration in patients with a poor response at surgery, tumour shrinkage leading to higher rates of complete surgical resection, and potentially greater immunological effect due to the presence of macroscopic tumour.[57] In a pooled analysis of patients who achieved an excellent pathological response, two-year recurrence-free survival rates of 96% and 79% with neoadjuvant ICI and targeted therapy, respectively, were demonstrated.[72] Despite this comparing favourably to the two-year recurrence-free survival of about 60% seen with adjuvant ICIs and targeted therapy, a head-to-head comparison of adjuvant versus neoadjuvant therapy is needed to explore which approach is most beneficial. Recently presented results from the phase 2 SWOG S1801 trial demonstrated that three cycles of neoadjuvant pembrolizumab followed by 15 cycles of adjuvant pembrolizumab is superior to 18 cycles of adjuvant pembrolizumab, with significantly better two-year event-free survival (72% *v* 49%; hazard ratio, 0.58; $P = 0.004$). These are the first data to suggest that neoadjuvant ICI may become the new standard of care over adjuvant ICI therapy.[73] Several other neoadjuvant trials are currently underway including the randomised phase 3 NADINA trial that is recruiting across multiple Australian sites (ClinicalTrials.gov, NCT04949113).[74] Neoadjuvant therapy represents an exciting prospect for the management of resectable disease, as patients may be able to receive only a few weeks of systemic therapy followed by surgery and then proceed to surveillance alone. It should be noted, however, that neoadjuvant therapy is currently limited to clinical trials.

Advances in supportive care

Due to the significant advances in melanoma treatment, numerous patients are now surviving many years, if not decades, after diagnosis. This has resulted in a new era of cancer care, involving melanoma survivorship, with a large community of survivors now coming together to contribute to and advance the management of melanoma. Several institutions across Australia actively involve consumers in research and education committees; for example, the Australian Melanoma Consumer Alliance consists of representatives from the Melanoma and Skin Cancer Advocacy Network, Melanoma Patients Australia, Melanoma Institute Australia, Melanoma and Skin Cancer Trials, the Australian Melanoma Research Foundation, Melanoma Research Victoria, Melanoma Western Australia and Melanoma Tasmania, with consumer groups reviewing research proposals and providing feedback.[75] This integration of consumers and of those affected by melanoma into research efforts reflects the fact that their insights and experiences are increasingly valued in improving the quality and relevance of research and models of care.[76]

A recent State of the Nation report jointly commissioned by Melanoma Institute Australia and Melanoma Patients Australia notes that, despite ongoing efforts to improve supportive care, there is much to be done.[77] Current challenges for all patients with cancer and long term survivors, not just those with melanoma, include lack of screening for supportive care, a shortage of disease-specific nurse consultants, no structured models for survivorship, and high out-of-pocket costs for long term survivors.[77]

Importantly, advances in supportive care require patient engagement to help with the design and creation of interventions. Treatment approaches need to adopt a holistic approach, with care for the whole person rather than just care of their cancer, and survivorship care plans should evolve into supportive care plans developed with the patient's input.[78]

Although survivorship is the accepted medical term, it is artificially defined to commence once treatment finishes and a patient transitions from active anticancer treatment to post-treatment care and disease surveillance.[79] However, the physical, emotional and financial implications begin at diagnosis, not after treatment completion, and thus supportive care plans should commence at diagnosis. Furthermore, support should be provided in a dynamic fashion, adapting as a person's quality of life indicators evolve and need change. This personalisation of supportive care focused on the whole person is not necessarily expensive. Once educated, and with appropriate supports from a nurse, or even trained volunteers, the patient is generally able to direct the right level of care they need.[80]

Melanoma management in the future

The management of cutaneous melanoma has been revolutionised in the past decade, with ongoing efforts to improve patient outcomes centred on rich translational research endeavours and robust clinical trials. Adoption of personalised risk assessment tools to tailor screening, treatment and surveillance will ensure appropriate escalation and de-escalation of care to provide the greatest benefit with minimal risk and toxicity, including physical, emotional and financial benefits. Decision-support tools are likely to become more reliable and accessible as algorithms derived from big datasets, including imaging, histopathology, genetic and outcome data, are validated in the clinical setting. In turn, reduced variability in diagnostic accuracy and management decisions will lead to earlier and more accurate melanoma detection and personalised approaches to treatment, with the ultimate goals of disease prevention and more efficient health system usage. Finally, the increasing

importance of consumer engagement cannot be overlooked. Encouraging patients to be involved in the development of their own management and supportive care plan will enable holistic care, leading to superior quality of life and clinical outcomes.

Acknowledgements: Prachi Bhave has received a National Health and Medical Research Council (NMHRC) postgraduate scholarship and an Australian Melanoma Research Foundation LEK Melanoma Research Grant. Anne Cust has received an NHMRC Investigator Grant (2008454). Victoria Mar is the recipient of an NHMRC Early Career Fellowship. The Australian Centre of Excellence in Melanoma Imaging and Diagnosis (ACEMID) has received funding from the Australian Cancer Research Foundation; an NHMRC Clinical Trials and Cohort Studies Grant (2001517); an NHMRC Centre of Research Excellence Grant (2006551); and an NHMRC Synergy Grant (2009923). No funding sources had a role in the planning, writing or publication of this work.

We acknowledge the contributions and guidance from Andrew M Haydon (Alfred Health, Monash University), B Mark Smithers (Princess Alexandra Hospital, University of Queensland), Peter Ferguson (Melanoma Institute Australia, University of Sydney, ACEMID), Caitlin Horsham (University of Queensland, ACEMID), Rodney Flude (Melanoma Institute Australia, ACEMID), Peter Soyer (University of Queensland, ACEMID), Rachael Morton (University of Sydney, ACEMID), Pablo Fernández-Peñas (Westmead Hospital, University of Sydney, ACEMID), Grant McArthur (Peter MacCallum Cancer Centre, University of Melbourne), and the ACEMID Consortium.

Open access: Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

Competing interests: Prachi Bhave has received conference sponsorship from Bristol-Myers Squibb (manufacturer of nivolumab), MSD (manufacturer of pembrolizumab) and Novartis (manufacturer of dabrafenib/trametinib), and speaker fees from Novartis and MSD. Victoria Mar has received speaker fees from Novartis, Bristol Myers Squibb, Merck and Janssen, and conference sponsorship from L'Oreal.

Provenance: Commissioned; externally peer reviewed. ■

1 Australian Institute of Health and Welfare. Cancer data in Australia [Cat. No. CAN 122]. AIHW, 2021. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/about (viewed May 2022).

2 Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for skin cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2016; 316: 429-435.

3 Whiteman DC, Olsen CM, MacGregor S, et al. The effect of screening on melanoma incidence and biopsy rates. *Br J Dermatol* 2022; 187: 515-522.

4 Watts CG, Dieng M, Morton RL, et al. Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review. *Br J Dermatol* 2015; 172: 33-47.

5 Cancer Council. Skin cancer incidence and mortality, 2016 [website]. https://wiki.cancer.org.au/skincancerstats_mw/index.php?title=Skin_cancer_incidence_and_mortality&oldid=630 (viewed June 2022).

6 Royal Australia College of General Practitioners. Guidelines for preventive activities in general practice; 9th ed. Melbourne: RACGP 2016. https://www.racgp.org.au/download/Documents/Guidelines/Redbook9/17048-Red-Book-9th-Edition.pdf (viewed June 2022).

7 Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. *Eur J Cancer Prev* 2015; 24: 141-149.

8 Watts CG, Cust AE, Menzies SW, et al. Cost-effectiveness of skin surveillance through a specialized clinic for patients at high risk of melanoma. *J Clin Oncol* 2017; 35: 63-71.

9 Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA* 2016; 315: 68-76.

10 Ford D, Bliss JM, Swerdlow AJ, et al. Risk of cutaneous melanoma associated with a family history of the disease. The International Melanoma Analysis Group (IMAGE). *Int J Cancer* 1995; 62: 377-381.

11 Aoude LG, Wadt KA, Pritchard AL, et al. Genetics of familial melanoma: 20 years after *CDKN2A*. *Pigment Cell Melanoma Res* 2015; 28: 148-160.

12 de Snoo FA, Hayward NK. Cutaneous melanoma susceptibility and progression genes. *Cancer Lett* 2005; 230: 153-186.

13 Taylor NJ, Mitra N, Qian L, et al. Estimating *CDKN2A* mutation carrier probability among global familial melanoma cases using GenoMELPREDICT. *J Am Acad Dermatol* 2019; 81: 386-394.

14 Law MH, Aoude LG, Duffy DL, et al. Multiplex melanoma families are enriched for polygenic risk. *Hum Mol Genet* 2020; 29: 2976-2985.

15 Landi MT, Bishop DT, MacGregor S, et al. Genome-wide association meta-analyses combining multiple risk phenotypes provide insights into the genetic architecture of cutaneous melanoma susceptibility. *Nat Genet* 2020; 52: 494-504.

16 Kaiser I, Pfahlberg AB, Uter W, et al. Risk prediction models for melanoma: a systematic review on the heterogeneity in model development and validation. *Int J Environ Res Public Health* 2020; 17: 7919.

17 Melanoma Institute Australia. Risk prediction tools [website]. Melanoma Institute Australia 2022. https://www.melanomarisk.org.au/ (viewed June 2022).

18 QIMR Berghofer Medical Research Institute. Melanoma risk predictor [website]. https://publications.qimrberghofer.edu.au/Custom/QSkinMelanomaRisk (viewed Mar 2023).

19 Mar V, Wolfe R, Kelly JW. Predicting melanoma risk for the Australian population. *Australas J Dermatol* 2011; 52: 109-116.

20 Vuong K, Armstrong BK, Weiderpass E, et al. Development and external validation of a melanoma risk prediction model based on self-assessed risk factors. *JAMA Dermatol* 2016; 152: 889-896.

21 Vuong K, Armstrong BK, Drummond M, et al. Development and external validation study of a melanoma risk prediction model incorporating clinically assessed naevi and solar lentigines. *Br J Dermatol* 2020; 182: 1262-1268.

22 Vuong K, Armstrong BK, Espinoza D, et al. An independent external validation of melanoma risk prediction models using the Australian Melanoma Family Study. *Br J Dermatol* 2021; 184: 957-960.

23 Olsen CM, Neale RE, Green AC, et al. Independent validation of six melanoma risk prediction models. *J Invest Dermatol* 2015; 135: 1377-1384.

24 Steinberg J, Iles MM, Lee JY, et al. Independent evaluation of melanoma polygenic risk scores in UK and Australian prospective cohorts. *Br J Dermatol* 2022; 186: 823-834.

25 Cust AE, Drummond M, Kanetsky PA, et al. Assessing the incremental contribution of common genomic variants to melanoma risk prediction in two population-based studies. *J Invest Dermatol* 2018; 138: 2617-2624.

26 Esdaile B, Mahmud I, Palmer A, et al. Diagnosing melanoma: how do we assess how good we are? *Clin Exp Dermatol* 2014; 39: 129-134.

27 Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. *BMJ* 2017; 357: j2813.

28 Corona R, Mele A, Amini M, et al. Interobserver variability on the histopathologic diagnosis of cutaneous melanoma and other pigmented skin lesions. *J Clin Oncol* 1996; 14: 1218-1223.

29 Cicchiello M, Lin MJ, Pan Y, et al. An assessment of clinical pathways and missed opportunities for the diagnosis of nodular melanoma versus superficial spreading melanoma. *Australas J Dermatol* 2016; 57: 97-101.

30 Australian Institute of Health and Welfare. Cancer in Australia 2021 [Cat. No. CAN 144]. Canberra: AIHW, 2021. https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2021/summary (viewed June 2022).

31 Glasziou PP, Jones MA, Pathirana T, et al. Estimating the magnitude of cancer overdiagnosis in Australia. *Med J Aust* 2020; 212: 163-168. https://www.mja.com.au/journal/2020/212/4/estimating-magnitude-cancer-overdiagnosis-australia#:~:text=Conclusions%3A%20About%2011%20000%20cancers,may%20be%20overdiagnosed%20each%20year

32 Welch HG, Mazer BL, Adamson AS. The rapid rise in cutaneous melanoma diagnoses. *N Eng J Med* 2021; 384: 72-79.

33 Udrea A, Mitra G, Costea D, et al. Accuracy of a smartphone application for triage of skin lesions based on machine learning algorithms. *J Eur Acad Dermatol Venereol* 2020; 34: 648-655.

34 Kelly JW, Yeatman JM, Regalia C, et al. A high incidence of melanoma found in patients with multiple dysplastic naevi by photographic surveillance. *Med J Aust* 1997; 167: 191-194. https://www.mja.com.au/journal/1997/167/4/high-incidence-melanoma-found-patients-multiple-dysplastic-naevi-photographic

35 MacKie RM, McHenry P, Hole D. Accelerated detection with prospective surveillance for cutaneous malignant melanoma in high-risk groups. *Lancet* 1993; 341: 1618-1620.

36 Mahumud RA, Janda M, Soyer HP, et al. Assessing the value of precision medicine health technologies to detect and manage melanoma. *Med J Aust* 2022; 217: 275-278. https://www.mja.com.au/journal/2022/217/6/assessing-value-precision-medicine-health-technologies-detect-and-manage

37 Haenssle HA, Fink C, Schneiderbauer R, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. *Ann Oncol* 2018; 29: 1836-1842.

38 Tschandl P, Rinner C, Apalla Z. Human-computer collaboration for skin cancer recognition. *Nat Med* 2020; 26: 1229-1234.

39 Janda M, Soyer HP. Can clinical decision making be enhanced by artificial intelligence? *Brit J Derm* 2019; 180: 247-248.

40 Kong FW, Horsham C, Ngoo A, et al. Review of smartphone mobile applications for skin cancer detection: what are the changes in availability, functionality, and costs to users over time? *Int J Derm* 2020; 60: 289-308.

41 Janda M, Horsham C, Vagenas D, et al. Accuracy of mobile digital teledermoscopy for skin self-examinations in adults at high risk of skin cancer: an open-label, randomised controlled trial. *Lancet Dig Health* 2020; 2: 129-137.

42 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 Derm* 2022; 158: 33-42.

43 Wada M, Ge ZY, Gilmore SJ, Mar VJ. Use of artificial intelligence in skin cancer diagnosis and management. *Med J Aust* 2020; 213: 256-259. https://www.mja.com.au/journal/2020/213/6/use-artificial-intelligence-skin-cancer-diagnosis-and-management

44 Daneshjou R, Smith MP, Sun MD, et al. Lack of transparency and potential bias in artificial intelligence data sets and algorithms: a scoping review. *JAMA Dermatol* 2021; 157: 1362-1369.

45 National Comprehensive Cancer Network. Melanoma: cutaneous. NCCN Clinical Practice Guidelines in Oncology; version 3, 2022. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf (viewed May 2022).

46 Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67: 472-492.

47 Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med* 2017; 376: 2211-2222.

48 Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2016; 17: 757-767.

49 Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; 355: 1307-1317.

50 Smithers BM, Saw RPM, Gyorki DE, et al. Contemporary management of locoregionally advanced melanoma in Australia and New Zealand and the role of adjuvant systemic therapy. *ANZ J Surg* 2021; 91: 3-13.

51 Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. *Ann Surg Oncol* 2018; 25: 2105-2110.

52 Bhave P, Haydon M. Treatment of high risk resected melanoma in Australia: current landscape and practises. *Aus J Derm* 2020; 61: 203-209.

53 Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial. *J Clin Oncol* 2019; 37 (Suppl): 2512.

54 Weber J, Del Vecchio M, Mandala M, et al. Adjuvant nivolumab (NIVO) versus ipilimumab (IPI) in resected stage III/IV melanoma: 3-year efficacy and biomarker results from the phase III CheckMate 238 trial. *Ann Oncol* 2019; 30 (Suppl): 533.

55 Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018; 378: 1789-1801.

56 Drummer R, Hauschild A, Santinami M, et al. Five-year analysis of adjuvant dabrafenib plus trametinib in stage III melanoma. *N Engl J Med* 2020; 383: 1139-1148.

57 Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. *Lancet* 2021; 398: 1002-1014.

58 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; 364: 2517-2526.

59 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-723.

60 Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol* 2015; 33: 1889-1894.

61 Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019; 20: 1239-1251.

62 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; 381: 1535-1546.

63 Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. *J Clin Oncol* 2021; 29 (Suppl): 9506.

64 Hodi FS, Chiarion-Sileni V, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. *J Clin Oncol* 2022; 40 (Suppl): 9522.

65 Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med* 2019; 381: 626-636.

66 Drummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018; 19: 1315-1327.

67 Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced *BRAF*(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; 17: 1248-1260.

68 Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): a phase III trial — ECOG-ACRIN EA6134. *J Clin Oncol* 2021; 39 (Suppl): 356154.

69 Ascierto PA, Mandalà M, Ferrucci PF, et al. Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated *BRAF*-mutated metastatic melanoma (SECOMBIT): a randomized, three-arm, open-label phase II trial. *J Clin Oncol* 2023; 41: 212-221.

70 Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet* 2022; 399: 1718-1729.

71 Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 2022; 386: 24-34.

72 Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med* 2021; 27: 301-309.

73 Patel S, Othus M, Prieto V, et al. Neoadjuvant versus adjuvant pembrolizumab for resected stage III-IV melanoma (SWOG S1801). *Ann Oncol* 2022; 33 (Suppl): S808-S869.

74 Lucas MW, Lijnsvelt J, Pulleman S, et al. The NADINA trial: a multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma. *J Clin Oncol* 2022; 40 (Suppl): TPS9605.

75 Melanoma Research Victoria. Australian Melanoma Consumer Alliance. https://melanomaresearchvic.com.au/australian-melanoma-consumer-alliance (viewed Mar 2023).

76 Domecq JP, Prutsky G, Elraiyah T, et al. Patient engagement in research: a systematic review. *BMC Health Serv Res* 2014; 14: 89.

77 State of the Nation. A report into melanoma — a National Health Priority; final report, February 2022. Insight Economics, 2022. https://melanoma.org.au/wp-content/uploads/2022/03/MIA-and-MPA_SoN-Report_Final-Report_28-March-2022.pdf (viewed Mar 2023).

78 Olver I, Keefe D, Herrstedt J, et al. Supportive care in cancer — a MASCC perspective. *Support Care Cancer* 2020; 28: 3467-3475.

79 Feuerstein M. Defining cancer survivorship. *J Cancer Surviv* 2007; 1: 5-7.

80 Lai-Kwon J, Kelly B, Lane S, et al. Feasibility, acceptability, and utility of a nurse-led survivorship program for people with metastatic melanoma (MELCARE). *Support Care Cancer* 2022; 30: 9587-9596. ■