We write regarding the following two manuscripts retracted from the June 2019 edition of Australian Journal of General Practice (AJGP).


In June 2019 the two papers we were invited to write by the Editor of the Australian Journal of General Practice (AJGP) were published in the journal. On July 4, 2019, Prof. John Thompson (Thompson) and others wrote a letter to the AJGP, asking that our papers be retracted as they allegedly contained significant errors.

The AJGP editor informed us that it was not necessary to respond to error allegations at the time, as the Thompson letter was not publishable because the it was not submitted in a form that met the journal requirements. To our surprise, our papers were subsequently retracted completely without our prior knowledge or input. The AJGP stated they had asked three independent experts to review the papers and that their evaluations supported retraction. We did not know of and were not permitted to respond to the reviewer’s concerns. Only in early January 2020 did the RACGP President, Dr Harry Nespelon provide us with the contents of their reviews. These reviews and our comments on these reviews are in Appendix 4.

We now address the concerns in the Thompson letter dated July 4, 2019.

Four preliminary comments on our manuscripts:

A. We were invited to write the two manuscripts by the AJGP Editor in Chief. We had not considered contributing to the journal prior to this request. We were initially asked just to write one paper, “Management of Invasive Melanoma”. When another group apparently withdrew from contributing a related manuscript, “Cutaneous Melanoma – Latest Developments”, the Editor asked us to also submit a review on this topic. The AJGP predetermined the manuscript titles when requesting this large task of our team.

B. Like all journals, the AJGP places many specific requirements on structure, word length, reference limitations, etc. The AJGP told us that there were four other commissioned manuscripts planned for the same special edition. We were advised of the requested focus of our papers and those of these additional papers, to minimize overlap. For example, dermoscopy was to be discussed in a manuscript by different authors. The limitation on the number of permitted references required us to cull over 20 references from each manuscript. Thus, important citations were removed to meet the journal specifications.
C. Our research team are volunteers. None of us are paid for our contributions to cutaneous oncology by state or federal governments. None of us receive direct or indirect support of any nature from any pharmaceutical company for any component of our cutaneous oncology research or teaching. In short, we are true independent volunteer researchers.

D. Our collective experience managing melanoma on a day to day basis spans over 100 years of practice. None of us perform sentinel lymph node biopsy or nodal ultrasound with or without fine needle biopsy. Between us we have hundreds of publications in major international peer reviewed journals. Our volunteer team of scientists bring an independent and truly objective academic review to management of melanoma. We review the research as scientists, not as clinicians with a conflicted interest in any particular drug or procedure.

The Complaints

There appear to be several main objections raised in the Thompson letter:

1. TGA APPROVALS. That we should have made it clear that following the MSLT2 trial results, the current Australian approval for melanoma drugs does not require lymph node clearance for patients to access adjuvant therapy. See pages 3 & 4

2. GUIDELINES. That we were incorrect when we stated in manuscript 1 that since 2008, “no updated formal evidence-based guidelines have been published in Australia”. See pages 5 - 15
   a. That we must have been aware of the Cancer Council’s clinical network melanoma guidelines (CGN guidelines) because we cited an article by Sladden et al, (reference 10) that was based on those same guidelines.
   b. That each set of the CGN guidelines is based on a systematic review
   c. That CGN guidelines are continuously updated
   d. That we were ignorant of the systematic process used to develop CGN guidelines
   e. That we were incorrect in stating that many recommendations in the CGN guidelines were little more than expert opinion with no evidence base.

3. SENTINEL NODE BIOPSY. That we were incorrect when we stated that, “Sentinel lymph node biopsy (SLNB) was not required in the management of any melanoma”. See pages 16 - 18
   a. That we ignored the strongly suggestive evidence from latent subgroup analysis of a large multicentre trial (MSLT1) that the survival outcome of node positive patients is substantially improved if the positive nodes are removed by SLNB. (Morton, 2014)
   b. That we misquoted MSLT2 trial results.
   c. That we failed to indicate that SLNB is the most reliable method of staging patients with T1B to T4 melanomas
   d. That when we stated that SLNB is not required we were providing advice contrary to all national and international guidelines.
   e. That we were unbalanced in stating SLNB had a 10% complication rate.
   f. That we were incorrect in claiming that SLNB is not an integral part of melanoma and should not become so unless and until a survival advantage is identified.

4. AJCC. That we failed to mention the AJCC melanoma staging system. See page 19

5. SECOND PRIMARY TUMOR. It is unclear to our team exactly what the Thompson letter objected to in our article. See page 20

6. EMINENT MULTIDISCIPLINARY TEAM. The contributors to the Thompson complaint letter (and also the CGN guidelines) are multidisciplinary eminent leading experts, including two General Practitioners. See page 20

7. FAILED TO MENTION SURGERY FOR MELANOMA SPREAD. That we were misleading when we stated in a key point that, “Melanoma that spreads to nodes or elsewhere can be managed with medication.” See pages 21 & 22
8. ULTRASOUND & FINE NEEDLE BIOPSY. That we were incorrect when we stated that, “Ultrasound and fine needle biopsy (USFNB) can diagnose nodal metastatic disease as accurately as SLNB”. See pages 23 - 26
   a. We erred when we failed to cite the recent article by Thompson et al (Ann Surg 2019) that the MSLT1 trial showed that of SLNB positive patients, only 7.1% had an abnormal preoperative ultrasound.
   b. That we were wrong to conclude that when performed by an experienced clinician, USFNB can be reliable in detecting early melanoma involvement.

9. MELANOMA DRUGS. That we inaccurately depicted the role and features of many melanoma drugs. We overstated their adverse events and understated their efficacy. See page 27 - 34

We shall address all of these complaints.
Our most serious concerns relate to points (1), (3a), (8) and (9) above.

We conclude on page 35.

Appendices:
1) APPENDIX 1 – PUBLISHED MANSCRIPTS ON US/ FNB FOR MELANOMA NODAL ASSESSMENT Page 36 & 37
2) APPENDIX 2 – AJGP reviews of our manuscript “Invasive melanoma management – March 6, 2019 Page 38 & 39
3) APPENDIX 3 – AJGP reviews of our manuscript – “Melanoma latest developments”- March 5, 2019 Page 40
4) APPENDIX 4 – The reviews following the Thompson letter and our point by point reply Page 41 - 47
5) APPENDIX 5 – Pertinent conflicts of interest of several authors of the Thompson letter Page 48
6) APPENDIX 6 – Conflict of interest declarations of authors of retracted manuscripts Page 49

(1) TGA APPROVALS. It is alleged that we should have been clear that once nodal disease is diagnosed, patients can get drug therapy without requiring lymph node clearance.

The Thompson letters states that our manuscript: “omits the critically important information that the current Australian approval, based on the results of MSLT-II, does not require lymph node clearance for patients to access adjuvant therapy and that lymph node clearance is not required for subsequent (NCT03068455) and ongoing adjuvant clinical trials.”

We have reviewed the public register for all melanoma drugs approved for usage in Australia by the Therapeutic Goods Administration, (TGA). As of January 24, 2020, there are three drug protocols approved by the TGA for nodal metastases that patients may receive only after complete resection.

1. Dabrafenib and Trametinib
   a. ARTG numbers: 205919, 205917 and 200922, 200936
   b. Approved indications: “Adjuvant treatment of melanoma. Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of the lymph node(s), following complete resection.’ And ‘Adjuvant treatment of melanoma. Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of the lymph node(s), following complete resection.’

2. Pembrolizumab
   a. ARTG numbers: 226597 and 263932
   b. Melanoma approved indications: “Pembrolizumab is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults. Pembrolizumab is indicated as monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.”

3. Nivolumab
   a. ARTG numbers: 231867 and 231868
b. Melanoma approved indications: “Nivolumab, as monotherapy is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Nivolumab, as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma. Nivolumab, in combination with ipilimumab is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).”

The TGA indications in all three cases clearly stipulate that complete resection of lymph node involvement is necessary to meet the requirements to prescribe these three agents. To our knowledge, the TGA has never approved a drug treatment for lymph node melanoma involvement that did not require nodes to be first resected if they were deemed resectable. The TGA confirmed to us by phone on January 24 2020 that complete node resection is required to access melanoma drugs when nodal involvement is diagnosed. The TGA explained that any other usage would be “off label”.

Along with the drugs listed above, the following drugs are approved by the TGA for management of melanoma. The list below details indications for which these agents have TGA approval as of January 2020.

- Encorafenib is indicated only for unresectable or metastatic melanoma
- Vemurafenib is only indicated for unresectable melanoma nodal disease stage IIIc and stage 4 melanoma
- Ipilimumab is indicated only for unresectable or metastatic melanoma
- Ipilimumab with nivolumab is indicated only for unresectable or metastatic melanoma.
- Cobimetinib with vemurafenib is indicated only for unresectable or metastatic melanoma.
- Binimetinib with encorafenib is indicated only for unresectable or metastatic melanoma.

**The Thompson letter is misleading in suggesting that complete resection is not required in SLNB positive patients in order to access approved melanoma drugs.**

There is the possibility that these specific details of TGA approvals are not widely known. At present melanoma patients might be offered these medications without being advised that their use without complete node dissection is “off label”.

Our statements in the paper were included with the belief that any education or information regarding “off label” usage of medications should clearly specify that the therapeutic agent is not approved in Australia for the specified indication. If patients are not advised that the therapy being offered is “off label”, this would suggest that patients are being denied vital information that may well affect their decision to accept or otherwise the offered therapy. We felt that general practitioners, the intended audience for our papers, should know how this pertained to the melanoma adjuvant therapies mentioned above.
2) GUIDELINES. That we should not have suggested that CGN guidelines lacked evidence base.

Prof. Thompson claims that the Cancer Council web site is evidence-based. We have pointed out many errors in the current Cancer Council guidelines.

The CGN section on SLNB (CGN-SLNB) contains significant errors, such that it can only be regarded as unbalanced and misleading.

There have been two seminal prospective multicentre randomized controlled trials (RCTs) to assess the long-term therapeutic benefit of SLNB as well as of subsequent complete lymph node dissection (CL), MSLT1 and MSLT2.

Together with a published Cochrane report, these three sources are our highest levels of evidence for the role of SLNB as a therapeutic intervention.

**MSLT1.**


**BACKGROUND:** Sentinel-node biopsy, a minimally invasive procedure for regional melanoma staging, was evaluated in a phase 3 trial. **METHODS:** We evaluated outcomes in 2001 patients with primary cutaneous melanomas randomly assigned to undergo wide excision and nodal observation, with lymphadenectomy for nodal relapse (observation group), or wide excision and sentinel-node biopsy, with immediate lymphadenectomy for nodal metastases detected on biopsy (biopsy group). Results **No significant treatment-related difference in the 10-year melanoma-specific survival rate was seen in the overall study population (20.8% with and 79.2% without nodal metastases).** Mean (+/- SE) 10-year disease-free survival rates were significantly improved in the biopsy group, as compared with the observation group, among patients with intermediate-thickness melanomas, defined as 1.20 to 3.50 mm (71.3 +/- 1.8% vs. 64.7 +/- 2.3%; hazard ratio for recurrence or metastasis, 0.76; P=0.01), and those with thick melanomas, defined as >3.50 mm (50.7 +/- 4.0% vs. 40.5 +/- 4.7%; hazard ratio, 0.70; P=0.03). Among patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1 +/- 4.8% among those with metastasis versus 85.1 +/- 1.5% for those without metastasis (hazard ratio for death from melanoma, 3.09; P<0.001); among patients with thick melanomas, the respective rates were 48.0 +/- 7.0% and 64.6 +/- 4.9% (hazard ratio, 1.75; P=0.03). Biopsy-based management improved the 10-year rate of distant disease-free survival (hazard ratio for distant metastasis, 0.62; P=0.02) and the 10-year rate of melanoma-specific survival (hazard ratio for death from melanoma, 0.56; P=0.006) for patients with intermediate-thickness melanomas and nodal metastases. Accelerated-failure-time latent-subgroup analysis was performed to account for the fact that nodal status was initially known only in the biopsy group, and a significant treatment benefit persisted. **CONCLUSIONS:** Biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy. Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease-free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas. (Funded by the National Cancer Institute, National Institutes of Health, and the Australia and New Zealand Melanoma Trials Group; ClinicalTrials.gov number, NCT00275496.)

The results as published have been heavily criticized as they play down the primary outcome for patients on an intention to treat basis. For melanoma patients in this trial with intermediate thickness primary disease, there was no significant survival difference over 10 years, with an non-significant improved survival figure for the intervention group.

In contrast, the study also showed, (though excluded from the abstract) that for patients with thick primary disease, there was no significant survival difference, **with a non-significant improved survival figure for the observation group.**

The post-hoc sub analyses of non-randomized patient groups have a very limited role, and in this case have been heavily criticized.

For example:

**BACKGROUND:** Sentinel lymph node biopsy (SLNB) was developed in the hope that it would improve outcomes for patients with melanoma. SLNB is an area of discussion and controversy in melanoma medicine. The final trial results of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) have now been published and the authors suggest their long-term results ‘clearly validate the use of sentinel-node biopsy in patients with intermediate-thickness or thick primary melanomas’. An accompanying editorial states that MSLT-I is a practice-changing trial. **CONCLUSIONS:** However, critical appraisal of MSLT-I data does not support the claims of the final report. On the contrary, **MSLT-I failed to demonstrate that there is a significant treatment-related difference in the 10-year melanoma-specific survival rate in the overall study population. Furthermore, there was no improvement in overall or melanoma-specific survival of the intermediate-thickness group (1.2-3.5 mm).** Completion lymphadenectomy can result in complications in about a third of patients, with a rate of clinically significant lymphoedema following axillary or groin dissection of 5-10%. Unnecessary lymphadenectomy can therefore have a major effect on patient quality of life. The evidence provided by Morton et al. does not support the claim that sentinel lymph node biopsy followed by lymphadenectomy in patients with positive sentinel nodes should be the standard of care in patients with melanoma. Readers are encouraged to check with registration sites to make sure declared primary outcomes are fairly reported. Post-hoc analyses are at best exploratory and cannot be used to form the principal conclusions of a trial.

Another senior academic surgical oncologist who was concerned that the authors were playing down the primary outcomes and relying instead on post-hoc data was Mr. Meirion Thomas. Thomas JM. Sentinel-node biopsy in melanoma. N Engl J Med 2014;370:2148.

**MSLT2.**

The second of the seminal RCT’s pertaining to the role of SLNB was the MSLT2 trial. In this trial all patients enrolled had a positive SLNB. They were then randomized into the intervention group which had completion lymph node dissection (CL) versus observation. There was no survival difference between the two groups.

The complete abstract is as follows:


Background Sentinel-lymph-node biopsy is associated with increased melanoma-specific survival (i.e., survival until death from melanoma) among patients with node-positive intermediate-thickness melanomas (1.2 to 3.5 mm). The value of completion lymph-node dissection for patients with sentinel-node metastases is not clear. Methods In an international trial, we randomly assigned patients with sentinel-node metastases detected by means of standard pathological assessment or a multimarker molecular assay to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). The primary endpoint was melanoma-specific survival. Secondary end points included disease-free survival and the cumulative rate of nonsentinel-node metastasis. **Results:** Immediate completion lymph-node dissection was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to-treat analysis or among 1755 patients in the per-protocol analysis. In the per-protocol analysis, the mean (+/-SE) 3-year rate of melanoma-specific survival was similar in the dissection group and the observation group (86+/-.13% and 86+/-.12%, respectively; P=0.42 by the log-rank test) at a median follow-up of 43 months. The rate of disease-free survival was slightly higher in the dissection group than in the observation group (68+/-.17% and 63+/-.17%, respectively; P=0.05 by the log-rank test) at 3 years, based on an increased rate of disease control in the regional nodes at 3 years (92+/-.10% vs. 77+/-.15%; P<0.001 by the log-rank test); these results must be interpreted with caution. Nonsentinel-node metastases, identified in 11.5% of the patients in the dissection group, were a strong, independent prognostic factor for recurrence (hazard ratio, 1.78; P=0.005). Lymphedema was observed in 24.1% of the patients in the dissection group and in 6.3% of those in the observation group. Conclusions Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. ( Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)
**COCHRANE REVIEW**

The third and final of the three sources for SLNB with the highest level of evidence is the published Cochrane review.


This analysis was completed after MSLT1 was published but before MSLT2 was published.

**BACKGROUND:** Melanoma is the leading cause of skin cancer-associated mortality. The vast majority of newly diagnosed melanomas are confined to the primary cutaneous site. Surgery represents the mainstay of melanoma treatment. Treatment strategies include wide excision of the primary tumour and sentinel lymph node biopsy (SLNB) to assess the status of the regional nodal basin(s). SLNB has become an important component of initial melanoma management providing accurate disease staging. OBJECTIVES: To assess the effects and safety of SLNB followed by completion lymph node dissection (CLND) for the treatment of localised primary cutaneous melanoma. **SEARCH METHODS:** We searched the following databases up to February 2015: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2015, Issue 1), MEDLINE (from 1946), EMBASE (from 1974), and LILACS ((Latin American and Caribbean Health Science Information database, from 1982). We also searched the following from inception: African Index Medicus, IndMED of India, Index Medicus for the South-East Asia Region, and six trials registers. We checked the reference lists of included and excluded studies for further references to relevant randomised controlled trials (RCTs). We searched ISI Web of Science Conference Proceedings from inception to February 2015, and we scanned the abstracts of major dermatology and oncology conference proceedings up to 2015. **SELECTION CRITERIA:** Two review authors independently assessed all RCTs comparing SLNB followed by CLND for the treatment of primary localised cutaneous melanoma for inclusion. Primary outcome measures were overall survival and rate of treatment complications and side effects. **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted and analysed data on survival and recurrence, assessed risk of bias, and collected adverse effect information from included trials. **MAIN RESULTS:** We identified and included a single eligible trial comparing SLNB with observation and published in eight different reports (from 2005 to 2014) with 2001 participants. This did not report on our first primary outcome of overall survival. The study did report on the rate of treatment complications. Our secondary outcomes of disease-specific and disease-free survival, local recurrence and distant metastases were reported. There were 1347 participants in the intermediate-thickness melanoma group and 314 in the thick melanoma group. With regard to treatment complications, short-term surgical morbidity (30 days) in 1735 participants showed no difference between SLNB and observation (risk ratio [RR] 1.11; 95% confidence interval [CI] 0.9 to 1.37) for wide excision of the tumour site but favoured observation for complications related to the regional nodal basin (RR 14.36; 95% CI 6.74 to 30.59). The study did not report the actual 10-year melanoma-specific survival rate for all included participants. Instead, melanoma-specific survival rates for each group of participants: intermediate-thickness melanoma (defined as 1.2 to 3.5 mm) and thick melanomas (defined as 3.50 mm or more) was reported. In the intermediate-thickness melanoma group there was no statistically significant difference in disease-specific survival between study groups at 10 years (81.4 +/- 1.5% versus 78.3 +/- 2.0%, hazard ratio [HR] 0.84; 95% CI 0.65 to 1.09). In the thick melanoma group, again there was no statistically significant difference in disease-specific survival between study groups at 10 years (58.9.3 +/- 4.1% versus 64.4 +/- 4.6%, HR 1.12; 95% CI 0.77 to 1.64). Combining these groups there was some heterogeneity (I^2 = 34%) but the total HR was not statistically significant (HR 0.92; 95% CI 0.74 to 1.14). This study failed to show any difference for its stated primary outcome. The summary estimate for disease-free survival at 10 years favoured SLNB over observation in participants with intermediate-thickness and thick melanomas (HR 0.75; 95% CI 0.63 to 0.89). With regard to the rate of local and regional recurrence as the site of first recurrence, a benefit of SLNB uniformly existed in both groups of participants with intermediate-thickness and thick melanomas (RR 0.56; 95% CI 0.45 to 0.69). This is in contrast with a uniformly unfavourable effect of SLNB with regard to the rate of distant metastases as site of first recurrence, in both groups of participants with intermediate-thickness and thick melanomas (HR 1.33; 95% CI 1.03 to 1.72). **AUTHORS’ CONCLUSIONS:** We contacted the trial authors querying the lack of data...
on overall survival which was the primary outcome of their important study. They stated “there are numerous additional analyses that have yet to be reported for the trial”. We expect that overall survival data will be available in a future update of this review. Disease-free survival and rate of local and regional recurrence favoured SLNB in both groups of participants with intermediate-thickness and thick melanomas but short-term surgical morbidity was higher in the SLNB group, especially with regard to complications in the nodal basin. The evidence for the outcomes of interest in this review is of low quality due to the risk of bias and imprecision of the estimated effects. Further research may have an important impact on our estimate of the effectiveness of SLNB in managing primary localised cutaneous melanoma. Currently this evidence is not sufficient to document a benefit of SLNB when compared to observation in individuals with primary localised cutaneous melanoma.

The CGN-SLN B mentions only one of the two RCTs on melanoma, - MSLT1.

The CGN-SLN B does not cite the Cochrane review but includes the following footnote:

“*A Cochrane review has been performed regarding the use of SLNB for melanoma (Kyrgidis et al). This review has not been cited in the evidence as the NHMRC recommendations for developers of guidelines suggest that a “systematic review should consist of at least two studies” (p. 16). The paper by Kyrgidis et al only cites a single study, the MSLT-1 study which is extensively discussed in the guidelines.”

In fact, the Kyrgidis team engaged two research reviewers to complete their systematic review. Hundreds of studies on SLN B for melanoma were evaluated. The reviewers predetermined that “all RCTs comparing SLNB followed by CLND for the treatment of primary localised cutaneous melanoma for inclusion”. The fact that only one study at that time was at the highest level of evidence to be detailed in their report is not a fault of this Cochrane review but indicates this review was undertaken correctly, and that the predetermined inclusion criteria was correctly applied.

It is noteworthy that the Cochrane review conclusions are very different than the CGN-SLN B conclusions. This must be of concern to anyone attempting to claim the CGN-SLN B is evidence-based and balanced.

Note the Cochrane review asked Prof Thompson and colleagues for added information of primary outcome data from MSLT1 trial. The MSLT1 research team refused to cooperate with the Cochrane review authors. The Cochrane review reported this non-compliance (above).

Of the three highest level of evidence sources on SLNB, the CGN-SLN B cites only one, MSLT1. It is for this reason that we stated that the CGN guidelines were not evidence-based.

In January 2020, a review of many formal Australian clinical guidelines identified that many recommendations in many guidelines lacked an evidence base.


BACKGROUND: Clinical practice guidelines aim to assist medical practitioners in making efficient evidence-based decisions in daily practice. However, international studies have shown that the majority of recommendations in American and European guidelines are not based on strong evidence. AIMS: To review Australian clinical practice guidelines across a broad range of high-impact conditions and determine how evidence-based they are. METHODS: Australian guidelines published from January 2010 to May 2018 relating to the top 10 causes of death in Australia were identified from the National Health and Medical Research Council (NHMRC) clinical practice guideline database and other relevant sources. The graded recommendations in these guidelines were extracted for analysis and the systems used for grading the recommendations were recorded. RESULTS: Ten relevant Australian guidelines were identified, containing a total of 748 graded recommendations. All 10 guidelines used either the Grading of Recommendations Assessment, Development and Evaluation (GRADE) or NHMRC systems to assess recommendations. However, only 18% (n = 136) of these recommendations were based on Level I (or equivalent) evidence; 25% (n = 185) were based on Level II evidence, 29% (n = 218) on Level III, and 9% (n = 66) on Level IV. Consensus-based recommendations accounted for 19% (n = 143) of all recommendations. CONCLUSIONS: Despite the enthusiasm of the evidence-based medicine movement and its documented successes, contemporary medicine appears to remain largely
evidence-poor, not evidence-based. Future research should aim to provide reliable descriptions of what constitutes valid clinical reasoning in evidence-poor situations.

This review covered the major causes of death in Australia. Melanoma was not included. The review included management of prostate cancer, colorectal cancer and lung cancer. It is apparent that other Australian cancer guidelines are lacking a suitable evidence base and that independent scientific reviews other than ours have identified same.

**NON-SURGICAL ALTERNATIVE OMISSION.**

Perhaps the greatest concern of the CGN-SLNB is its omission of any information regarding non-surgical options to SLNB. Given the evidence that SLNB provides prognostic information but that a therapeutic advantage has not been identified, there may be other methods of obtaining that same prognostic advice regarding early nodal involvement of melanoma. Later, in the section on “Ultrasound” we identify non-surgical alternatives. These may be less reliable than SLNB in detecting early melanoma nodal involvement. But they remain non-surgical alternatives that have been demonstrated in large international trials. As such, no balanced discussion of SLNB could be undertaken without mentioning and analysing the non-surgical alternatives.

It is a core requirement in obtaining informed consent for a surgical procedure that the proceduralist offer non-surgical alternatives if any exist. It is a serious omission of CGN-SLNB that these details are absent. This could lead the reader to mistakenly assume they don’t exist. Such would result in patient’s failing to receive valid informed consent when the SLNB surgical procedure is offered to them.

**INCLUSION OF LOW-LEVEL EVIDENCE.**

The CGN-SLNB devotes considerable text to identifying other risk factors which may or may not alter the likelihood of sentinel node positivity. Many of the cited studies evaluated univariate data. The following were included citations in CGN-SLNB.


Univariate data usually do not meet the quality criteria for inclusion in a peer-reviewed systematic review. Such a level of evidence would certainly not be included in a systematic review of SLNB given that quality multivariate data are available, as provided in the MSLT1 study. Most of this large section of the CGN-SLNB needs to be revised, focusing on the multivariate analysis of survival risk factors identified in MSLT1. Indeed, in our manuscripts we highlighted this valuable multivariate data.

**DIFFERENCES OF OPINION ARE NO REASON FOR RETRACTION**

The Cancer Council and Thompson and colleagues may have a different view regarding whether their CGN-SLNB is suitably evidence based. We detail above a valid case that the CGN-SLNB is insufficiently evidence-based to qualify as an evidence-based formal national guideline.
A different view on whether the CGN-SLN B evidence-base is no reason for retraction.

**COPE guidelines** on reasons for retraction of a published manuscript are as follows:

Editors should consider retracting a publication if:

- They have clear evidence that the findings are unreliable, either as a result of major error (eg, miscalculation or experimental error), or as a result of fabrication (eg, of data) or falsification (eg, image manipulation)
- It constitutes plagiarism
- The findings have previously been published elsewhere without proper attribution to previous sources or disclosure to the editor, permission to republish, or justification (ie, cases of redundant publication)
- It contains material or data without authorization for use
- Copyright has been infringed or there is some other serious legal issue (eg, libel, privacy) • It reports unethical research
- It has been published solely on the basis of a compromised or manipulated peer review process
- The author(s) failed to disclose a major competing interest (a.k.a. conflict of interest) that, in the view of the editor, would have unduly affected interpretations of the work or recommendations by editors and peer reviewers.

Retractions are not usually appropriate if:

- The authorship is disputed but there is no reason to doubt the validity of the findings
- The main findings of the work are still reliable and correction could sufficiently address errors or concerns
- An editor has inconclusive evidence to support retraction, or is awaiting additional information such as from an institutional investigation (for information about Expressions of Concern see [https://publicationethics.org/expressions-of-concern-forum-discussion](https://publicationethics.org/expressions-of-concern-forum-discussion))
- Author conflicts of interest have been reported to the journal after publication, but in the editor’s view these are not likely to have influenced interpretations or recommendations or the conclusions of the article.

Clearly none of the circumstances for retraction apply for either of our manuscripts. Certainly, the editor did not have conclusive “evidence to support retraction”.

A **difference of opinion** is a basis for The Cancer Council to write a formal letter to the journal editor expressing their view that their guidelines are accurate and evidence based. It is no reason to retract our manuscript.

2a. **SLADDEN CITATION:** Thompson letter advises we must have known of the CGN guidelines because we cited a paper by Sladden et al (MJA 2018) that was based on the guideline.


The Medical Journal of Australia is a peer reviewed journal. We hence know this manuscript has been through an appropriate peer review process with reviewers blinded as to author identity. We were correct in citing the updated margin of clearance recommendation from a peer reviewed journal. We would not have cited from a source that was non-independent, and had not undergone blinded peer reviewed.

A/Prof. Mike Sladden was on the working group that established the CGN guidelines.

He was also part of the team working on the CGN-SLN B. The team did not reach consensus. A/Prof. Mike Sladden advised the working group (as well as ACCO) that he “withdrew his support for the final version of SLNB guidelines because he did not think it provided a balanced point of view”.

The CGN guideline fails to mention this, or indeed any suggestion that the SLNB section was anything other than universally endorsed. Of course, this alternative position by Sladden would be well known to Prof. Thompson and the Cancer Council itself.
2b. DEFINITION OF SYSTEMATIC REVIEW: “The CGN guidelines were based on systematic reviews.”

A systematic review is a well-defined entity in medical research. The British Medical Journal in 1997 published a summary of a systematic review versus a met-analysis.

- Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). BMJ 1997;315:672-5.

A systematic review must be conducted in a specific defined manner. It requires a defined question to be answered.

The methodology must be rigorously designed. An eligibility criterion must be predetermined. Levels of evidence of studies to be included is specified in the methodology before the literature search commences. If there have been RCTs completed to address the review question, these will be the core of the review. For any RCT, the findings of the primary outcome on an intention to treat basis is the key data for analysis. Post-hoc data from RCTs is not generally included as it can be very misleading. If there are prospective large RCTs a systematic review would typically exclude non-randomized trials or any retrospective trials.

Once the question and eligibility criteria is defined, a thorough literature search begins. Hundreds of even thousands of manuscripts might be included in the process to determine whether or not the eligibility criteria have been met on a study by study basis. Out of such studies, very few may meet the eligibility criteria. Studies that do not meet the criteria are not included in the review thereafter. Reviewers will take into account whether the randomization is blinded / double blinded. They will examine for possible biases in population selection. The completed review must be published and available for open review in full. This must include detailing the methodology and inclusion criteria.

Greenhalgh compares and contrasts a systematic review with a meta-analysis. A meta-analysis cannot be based on a single study. However, a systematic review could be based on a single study if only one study meets the predetermined eligibility criteria.

Thompson claims the CGN guidelines were based on many systematic reviews. The authors of the SLNB section also state that they completed a “systematic review” of SLNB and that the CGN-SLNb summarises their review. We have not been advised of the methodology or inclusion criteria.

As of January 30 2020, no such systematic review of SLNB has been published in a peer reviewed journal by the CGN-SLNb authors. The completeness and objectivity of their systemic review cannot be substantiated. The claim of completing a “systematic review” should not be made until such time as it is verified that an independent peer reviewed journal has published such a systematic review. It is apparent that this CGN-SLNb guideline would not be accepted by an authoritative peer reviewed journal until such time as the major inadequacies we have identified have been addressed.

2c. The CGN guidelines are continually updated

Whilst we would expect this to be the case, we note that the SLNB section has not been updated since we identified the above deficiencies. On January 30, 2020 the CGN-SLNb section details that it was last modified on May 17, 2018.

2d. We were ignorant of the systematic process

We have outlined above our knowledge of the process, including the claims of completing a systematic review as well as the way the expertise of A. Prof. Sladden was managed in the process.

2e. We were incorrect to suggest some of CGN guidelines were little more than expert opinion.

COMPLICATION RATES FROM SLNB

One of the recommendations in the CGN-SLNb is as follows:

“Complication rates for sentinel lymph node biopsy are low. The procedure should be performed in a centre with appropriate expertise as complication rates are inversely related to procedure volume - this particularly applies to primaries arising in the head and neck.”

The CGN-SLNb cites two studies as the basis for this recommendation.
For patients with melanoma metastasis to a sentinel lymph node, subsequent complete regional lymph node dissection (CLND) is currently regarded to be the surgical standard. This approach, however, has not been confirmed by controlled studies, so that surgical morbidity is of primary importance. Using clinical examination and a questionnaire, we determined morbidity in 315 patients with axillary or inguinal lymph node excision on whom 275 sentinel lymphadenectomies (SLNEs) and 90 CLNDs were performed. The overall incidence of at least one complication following SLNE was 13.8%. The short-term complication rate was 11.3% (allergic reaction to blue dye 0%, wound breakdown 0%, haematoma 2.5%, wound infection 3.6%, seroma 6.9%). The incidence of long-term complications was 4.1% (persistent tattoo 0.4%, functional deficit 0.4%, nerve dysfunction/pain 0.7% or swelling 2.5%). All complications were mild. Significantly, the complication rate was not higher for patients aged 70 years or older. After CLND, the overall complication rate was significantly higher (65.5%, P<0.00001). The incidence of short-term complications was 50% (haematoma 0%, wound breakdown 6.7%, wound infection 24.7% or seroma 34.8%). The incidence of long-term complications was also 50% (nerve dysfunction/pain 8.9%, functional deficit 16.8%, swelling 37.1%). Overall, inguinal lymph node excision was burdened by a higher complication rate (P=0.015). Age and sex did not influence postoperative morbidity. No deaths linked to either procedure were noted. Complication rates after SLNE are low and most complications are minor and short-lasting. In contrast, CLND has been demonstrated to be a major and potentially morbid surgical procedure. This highlights the importance of testing the therapeutic value that CLND adds to the sentinel lymph node procedure.


BACKGROUND: Sentinel lymph node biopsy has become routine in the staging of patients with cutaneous melanoma and is presumed to have fewer complications than elective regional lymph node dissection (RLND). However, little information is available to refute or support this assumption. HYPOTHESIS: Risk factors for complications following sentinel lymph node biopsy (SLNB) can be identified. DESIGN: Retrospective medical record review. PATIENTS AND METHODS: The medical records of 339 consecutive patients undergoing SLNB for melanoma between 1996 and 2003 at our institution were reviewed for complications. RESULTS: In our series of 339 patients, 20 complications (5.9%) were observed following SLNB compared with 15 (19.5%) of 77 patients undergoing RLND during the same period (P<0.001). Seroma formation, transient nerve injuries, and minor wound infections were the most frequently observed complications in patients undergoing SLNB. In contrast, chronic lymphedema and wound infections were the most frequent complications observed in patients undergoing RLND. Patients with comorbid medical conditions had more complications following either SLNB or RLND than those without. The number of lymph nodes excised and the placement of closed-suction drainage were associated with an increased incidence of complications following SLNB but not RLND. The incidence of annual complications inversely correlated with the cumulative number of SLNBs performed during this period. CONCLUSIONS: Sentinel lymph node biopsy can be performed with a low incidence of complications. Experience with SLNB decreases complications. Patients with more than 1 sentinel lymph node excised or a closed-suction drain placed at the time of SLNB are at an increased risk of complications.
series of 339 patients, 20 complications (5.9%) were observed following SLNBX compared with 15 (19.5%) of 77 patients undergoing RLND during the same period (P<.001). Seroma formation, transient nerve injuries, and minor wound infections were the most frequently observed complications in patients undergoing SLNBX. In contrast, chronic lymphedema and wound infections were the most frequent complications observed in patients undergoing RLND. Patients with comorbid medical conditions had more complications following either SLNBX or RLND than those without. The number of lymph nodes excised and the placement of closed-suction drainage were associated with an increased incidence of complications following SLNBX but not RLND. The incidence of annual complications inversely correlated with the cumulative number of SLNBXs performed during this period. CONCLUSIONS: Sentinel lymph node biopsy can be performed with a low incidence of complications. Experience with SLNBX decreases complications. Patients with more than 1 sentinel lymph node excised or a closed-suction drain placed at the time of SLNBX are at an increased risk of complications.

The authors also failed to cite this 2017 systematic review of SLNB complications:


PURPOSE: The complications reported after sentinel lymph node biopsy (SLNB) for melanoma is highly variable in the worldwide literature; the overall complication rate varies between 1.8% and 29.9%. With heterogeneous reporting of morbidity data, no 'average' complication rates of this procedure have been reported. This systematic review aims to determine the complications rates associated with SLNB. METHODS: A systematic review of English-language literature from 2000 to 2015, which reported morbidity information about SLNB for melanoma, was performed. The methodological quality of the included studies was performed using the methodological index for non-randomised studies (MINORS) instrument and Detsky score. Pooled proportions of specific post-operative complications were constructed using a random effects statistical model, and subgroups including lymph node basin and continent of origin of the study were compared. RESULTS: After application of inclusion and exclusion criteria, 21 articles progressed to the final analysis. 9047 patients were included. The overall complication rate was 11.3% (95% CI: 8.1-15.0). The incidence of infection was 2.9% (95% CI: 1.5-4.6); seroma 5.1% (95% CI: 2.5-8.6); haematoma 0.5% (95% CI: 0.3-0.9) lymphoedema 1.3% (95% CI: 0.5-2.6) and nerve injury 0.3% (95% CI: 0.1-0.6). There was no statistically significant difference in morbidity between the sites of SLNB or between continents. DISCUSSION: This study provides information about the incidence of complications after SLNB. It can be used to counsel patients about the procedure and it sets a benchmark against which surgeons can audit their practice.

The authors cited two small studies. One of these was a file review and the other a retrospective study. In contrast, the Morton study was prospective and multicenter.

Including the studies and not cited by the authors, there is no statistical evidence to support the claims of procedural volume and head and neck aspects of outcome.

In 2019 the following study was published.


This study of 886 patients was retrospective but powered to detect significant differences on population subgroups. This study identified the inguinal region (not head and neck) as a risk factor for greater adverse outcome incidence.

The CGN – SLNB guideline; “Complication rates for sentinel lymph node biopsy are low. The procedure should be performed in a centre with appropriate expertise as complication rates are inversely related to procedure volume - this particularly applies to primaries arising in the head and neck.”

It is misleading for the Thompson letter to suggest the complication rate of SLNB is “low”. A surgical complication rate of 10 – 11% could not be considered low. The comments on expertise and head and neck risk have no evidence base. If
anything, the inguinal region could be argued was a particular site of concern. The complication rate versus procedural volume claim has no supportive data.

To substantiate their “low” complication claim, the authors chose to cite a SLNB retrospective study of 339 patients in which a post-operative complication rate of 5.9% was reported (Roaten, above). Note that the systematic review (above) included 21 studies with over 9000 patients and found an average complication rate of 11.3%. Selecting the Roaten study as one of only two references was cherry picking from available data. This indicates bias not acceptable in a systematic review. If there was any publication cited in a systematic review of SLNB for analysis of complications, it would be the Moody review above.

The comment that complications are “low” without stating a figure is misleading. The complication rate from Ultrasound and fine needle biopsy (FNB) is less than 1%.


Compared to Ultrasound and FNB, a 10%+ complication is very high. The guidelines should be accurate and quote figures. The reader may misconstrue the comment of “low” as being comparable to the non-surgical alternatives. As the suggestion that complications of SLNB are “low” is not supported by a literature review, it can best be regarded as simply expert opinion.

COUNSELLING PATIENTS REGARDING SLNB

The CGN-SLNB recommends that “Patients being considered for sentinel lymph node biopsy (SLNB) should be given an opportunity to fully discuss the risks and benefits with a clinician who performs this procedure”.

This statement is over-simplistic and can only be regarded as expert advice.

There is no doubt that a surgeon has an obligation to provide informed consent prior to undertaking any operation, including SLNB. As such, any patient who is referred for consideration of SLNB needs to have an opportunity to discuss the risks and benefits with a clinician who performs the procedure.

There are several alternatives for the patient with a newly diagnosed melanoma. The GP considering referral would likely wish to discuss with the patient the available options for detecting possible nodal involvement or not detecting early nodal involvement. Ideally, the GP would discuss both surgical and non-surgical options for assessing nodal involvement and hence future mortality risk assessment. This is the point where a patient is likely to be considered for SLNB, imaging or the other options.

There is no doubt that any medical imaging consultant has an obligation to provide informed consent prior to undertaking a nodal ultrasound and FNB.

The guideline currently only suggests that patients being considered for SLNB should be given the opportunity to discuss the procedure with the clinician performing this test. If there are other options available, and the same logic is applied, the guidelines must suggest that patients be given the opportunity to discuss both surgical and non-surgical alternatives with the various proceduralists that perform each. The advice given in CGNB-SLN is internally inconsistent.

Quality guidelines would assist GPs at the point of explaining the new diagnosis of primary melanoma to patients. The GP will discuss options. Some patients may choose to first explore the SLNB option. Others may choose to first explore the USFN option. Others may choose neither of these future risk evaluations. It is not appropriate to suggest the GP must refer patients to a surgeon who undertakes SLNB.
We are mindful here of the isolated rural patient and their rural GP. In many cases the melanoma is likely to be managed by the well-trained GP or rural General Surgeon in their local setting. The discussion between the doctor and the patient should also include the role of SLNB, USFNB and other options. In many circumstances the patient may consider the extensive travel to a large centre not appropriate or them. It may not be affordable.

The situation would be different if there was an evidence base demonstrating that certain clinicians are far better than others at explaining the pros and cons of SLNB. We are not aware of any study being completed that demonstrates that advice on those matters from one type of clinician is superior to advice from others. The CGN-SLN B authors do not cite such a clinician difference.

This guideline is merely expert opinion. It appears to be self-serving expert opinion. Surgeons that regularly undertake SLNB are conflicted in that they perform the procedure, which could cloud objectivity.

This recommendation places GPs, particularly rural and remote GPs, in an invidious position. Suggesting the reasonable options to their new melanoma patients could be now viewed as insufficient. Are rural doctors to feel obliged to refer their patients some distance to discuss an operation that does not alter survival with a surgeon that undertakes that procedure?

We agree that many sections of the CGN guidelines are of a standard well above the CGN-SLN B section. Each section relies on the other to make the whole. In this context, the CGN-SLN B appears to be the weakest link in the chain.
3) **SENTINEL LYMPH NODE BIOPSY. We should not have suggested that SLNB is not required**

This is the major controversy for Prof. Thompson. He is a strong proponent of SLNB. We are at a loss as to how he can argue that SLNB is “required”. We believe we are justified in our view that the scientific literature demonstrates that SLNB is not required in the management of melanoma. The only intervention that should be considered required for primary melanoma treatment is wide local excision (WLE).

When it was clear that SLNB offered no survival benefit based on the results of a large RCT on an ITT basis, it was correct for us to make it clear to GPs that SLNB is not required. While we agree with Thompson that SLNB provides valuable prognostic information, gaining that information through SLNB or other tests cannot be regarded as a requirement.

The Thompson letter suggests our views on SLNB are the isolated beliefs of a single uninformed group of authors and are contrary to the rest of global thinking. National guidelines do recommend, but do not require SLNB. Moreover, both the Cochrane review and the Medicare Specialist Advisory Committee, (MSAC) agree with our viewpoint.

MSAC were asked by surgeons to add to the current Medicare benefits an item number of suitable increased value specifically for SLNB on melanoma patients. The summary in brief of MSAC to the Federal Minister of Health, (Hon Greg Hunt) is as follows:

> “After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on MBS funding for SLNB for intermediate thickness and thick cutaneous melanoma.

> MSAC did not accept the rationale for a fee increase for a SLNB-specific MBS item, compared to the current non-specific MBS items under which this service is currently being claimed, since there was insufficient evidence of a difference in patient health outcomes or clinical management as a consequence of using SLNB compared to not using it.

> While MSAC acknowledged the prognostic value of SLNB in staging of melanoma and the potential for this to determine patient access to adjuvant therapies, MSAC deferred its advice to request further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNB in selecting patients for such treatment.”

Moreover, other cutaneous oncology research teams have also expressed concerns with current SLNB usage. For example:


In addition, we have also expressed our viewpoint previously:


There have been hundreds of studies on SLNB. In a systematic review of these, one would look for any metaanalyses, any large prospective randomized controlled trials and existing high levels systematic reviews such as Cochrane Review. We have detailed the papers that would be identified as of highest level of evidence in (2) above.
MSLT1 randomized controlled trial compared SLNB and elective node dissection to simple observation. Over ten years, no survival difference was found on an intention to treat basis.


MSLT2. This trial enrolled patients who had melanoma and were SLNB positive.


Patients were randomized into node dissection versus observation. Again, there was no survival difference between observation and intervention groups. The trial found there was no benefit in excising remaining nodes if a SLNB was found to be positive.

Above in (2) we have also detailed the Cochrane Review on SLNB.


The completed Cochrane review concluded, as we have, that a patient benefit from SLNB cannot be established.

We believe the evidence is clear. Numerous studies of SLNB demonstrated there is no identifiable SLNB survival advantage, whether or not subsequent complete node dissection was performed. Lower evidence level studies, such as from retrospective trial and studies without control groups could not be properly included in any systematic review of SLNB, given that existing higher-level data is abundant.

### 3a. We ignored the latent group analysis in MSLT1

The final report of the MSLT1 trial details a latent sub-group analysis. The patients are not compared on intention to treat (ITT) basis. The analysis compares patients who had a positive SLNB and subsequent node dissection with patients in the non-biopsy group. Based on his analysis of this subgroup, Thompson continues to suggest that SLNB positive patients survive better than those with nodes presenting later.

His analysis excluded patients who were SLNB negative but later developed lymph node involvement. They were left out of the MSLT1 positive SLNB population. Yet, on the observation arm all patients that developed nodes were included. Those who had undergone SLNB and completion lymphadenectomy were deemed to be “disease free”.

As such, his intervention analysis comparison compares true positive SLNB patients as well as false positives, while excluding false negatives, - with all patients in the observation arm.

The latent group comparison, as Azzopardi et al (above) point out, is like comparing apples to antelopes. This MSLT1 subanalysis simply show that SLNB has inaccuracies. There are both false positives and false negatives. As with any test, SLNB is not perfect.

The outcomes that are valid are those on an ITT basis. SLNB does not alter survival. Prof. Thompson is an author of MSLT1 and MSLT2. We were correct to not include post hoc invalid subanalyses of an RCT in our manuscripts.

### 3b. We misquoted MSLT 2 trial.

Our summary of the MSLT2 trial is as follows in our Melanoma: Latest Developments manuscript.

“*The MSLT2 trial randomised patients who had a positive sentinel node into those having completion lymphadenectomy versus observation. Once again, no survival benefit was identified*”.

We correctly identified the patients that were in the intervention group rather than the control group. We correctly identified that no survival difference was identified. There was no misquote. This is what the primary trial outcome of MSLT2 identified.

### 3c. We failed to identify that SLNB is the most reliable method of staging patients.
We made it clear in both manuscripts that SLNB provided very good prognostic advice through its role in identifying early nodal disease. That is what is being achieved with “staging”. We are not sure of what Prof. Thompson’s concern is here. Did Thompson simply not like the wording we used? We did not inaccurately identify SLNB’s benefits as an independent predictor of outcome.

Important here is the term “most reliable”. Thompson accurately confirms that there are other methods, such as we identify below in the Ultrasound section. As we highlighted in (2) above, whether or not a non-surgical approach to staging is as reliable as SLNB is not relevant. There is an ethical need to offer patients a non-surgical option. In the balanced discussion with a patient regarding SLNB, it and non-surgical alternatives need to both be discussed, and the relative accuracy of each is a part of that required discussion.

3d. We contradict all national and international guidelines

The Thompson letter says that our claim that “SLNB” is not required is contrary to all national and international guidelines. We have already described the basis for our view that SLNB is not “required.” Although national guidelines suggest consideration of or suggest offering some melanoma patients SLNB, we are not aware of any national or international guidelines that require SLNB. The onus here is on Prof. Thompson to support this claim. We believe it cannot be done.

3e. That we were unbalanced in stating that SLNB had a 10% complication rate.

A 10% complication rate was the findings of the MSLT1 trial.


Thompson was an author of this manuscript. This is not unbalanced. It is fact.

By quoting this figure we were being conservative. As pointed out above, the systematic review of SLNB identified a complication rate over 11% in 21 studies of over 9000 patients that had undergone SLNB.


3f. We should not suggest that “SLNB is not an integral part of melanoma management and should not become so until a survival advantage is identified.”

We disagree with this suggestion by Thompson. Surgery is an integral part of cancer management when it has a demonstrated survival advantage compared to non-surgical alternatives or observation. This is clearly not the case with SLNB. Nor can SLNB be regarded as “integral” to melanoma risk assessment when other methods of risk assessment are available, including USFN B. (See Ultrasound, below)
4) **AJCC STAGING: We should have mentioned the AJCC staging system**

Another set of excellent data that was produced in the MSLT1 trial was analysis of risk factors for poorer prognosis in melanoma patients. These were shown to be: Breslow thickness, nodal involvement, distal metastases, tumour location and the presence or absence of ulceration in the primary tumour.

It was our view most GPs likely were familiar with the fact that spread to nodes or elsewhere resulted in a higher mortality risk. GPs may not have been as familiar with the ulceration and location risk factors. As such, we chose to highlight these independent risk factors in the manuscripts. Of course, Breslow thickness remains the single most important risk predictor. The following table is extracted from our first manuscript, *Managing Melanoma*.

**What factors in a new melanoma alter melanoma specific survival (based on multivariate analysis)**

<table>
<thead>
<tr>
<th>Factors that worsen survival</th>
<th>Factors that do not alter survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>Clark level</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>Gender</td>
</tr>
<tr>
<td>Breslow thickness of primary tumour</td>
<td>Age</td>
</tr>
<tr>
<td>Ulceration in primary tumour</td>
<td>Closure of defect technique</td>
</tr>
<tr>
<td>Primary tumour located on the trunk</td>
<td>Primary location on limbs or head and neck</td>
</tr>
</tbody>
</table>

We also wanted to advise GPs that Clark level was no longer considered necessary and was not an independent predictor of outcome.

The AJCC system assesses Breslow thickness, primary tumour ulceration, nodal involvement, or distant metastatic disease.

Given word count and reference limitation, we taught the core knowledge of aspects of a melanoma that predicted survival. It was our view that this was the key information GPS needed to know. How that translates into a code such as the AJCC staging system was secondary. The specialists that GPs refer to would be expected to know the AJCC code system. GPs with a greater involvement in melanoma management would be expected to already know the AJCC staging system. We teach this to such GPs. It is also on our web site.

5) SECOND PRIMARY. It is unclear what the allegation is here, as the letter states that our article “makes incorrect statements and omits critical information. We are unaware of anecdotes regarding second primary melanoma not being managed with excision in patients being treated with the agents discussed.”

The authors of the Thompson letter may well dispute that any patients are being advised that WLE of a second primary melanomas is not required. However, Prof. Anthony Dixon has experienced this misconception in managing melanoma referrals from GPs and when presenting melanoma lectures to GPs. Dr. Dixon repeatedly found himself explaining that it was still important to widely excise new primary melanomas despite patients concurrently receiving melanoma drug therapy. Our team felt it was necessary to dispel this very serious misconception and included it in our manuscript. Simply, Prof Thompson’s anecdotal lack of experience of this situation does not invalidate Prof Anthony Dixon’s anecdotal experiences.

6) MULTIDISCIPLINARY EMINENCE. The need for prominent multidisciplinary experts to write manuscripts such as these.

The Thompson letter suggests that our team has inadequate training and experience to write melanoma review manuscripts. (Note that the AJGP chose us to write the articles, including the second “Latest Development” paper after a different team withdrew).

We were said to lack their multidisciplinary background. Our team includes:

- Prof. Anthony Dixon. Until recently Anthony was in full time referral based cutaneous oncology practice in Geelong for 20 years. This included daily managing melanoma patients. On average, Anthony had 60 new melanoma patient referrals from GPs each year. Anthony has a PhD and over 20 years research experience pertaining to complications and outcomes of skin cancer management. Anthony has an honorary dermatology degree and is a Professor within the AOCO organization in the USA. He has over 25 years’ experience teaching GPs, having taught over 2000 GPs at workshops in Australia and New Zealand apart from his role educating dermatologists and dermatology trainees in USA and elsewhere.

- Prof. John Dixon has over 25 years’ experience in evidence-based medicine including high level drugs trials. John also has a PhD and other specialist degrees. John has published major trials in the world’s leading journals. Before a full-time career in medical research, John was a rural General Practitioner. He can mix the science with the grass roots experience.

- A. Prof. Howard Steinman is a dermatologist and fellowship trained Mohs surgeon in USA whose practice is limited to cutaneous oncology. Howard has over 30 years’ experience in full-time skin cancer management including managing melanoma patients. He is also an Associate Professor in Surgery in USA. Howard was a pioneer in Mohs surgery and skin cancer education for dermatologists and dermatology residents in USA. He co-founded the American Society of Mohs Surgery, an education entity responsible for training many post graduate dermatologists in skin cancer management, including melanoma.

- Dr. Alexander Nirenberg is a dermatopathologist dealing only with skin disease in Melbourne. Dr. Nirenberg has extensive teaching experience including teaching GPs in Australia relevant dermatopathology for their needs.

- Dr. Stuart Anderson is a rural GP in Maffra, Victoria. Stuart has a major interest in skin cancer including melanoma. He is a Fellow of the Australasian College of Cutaneous Oncology as well as a Fellow of the RACGP, with a Fellowship in Advanced Rural General Practice (Surgery). He has extensive experience teaching GPs as a Medical Educator and in knowing what it is that GPs need to know.

Our team has collectively published many hundreds of manuscripts in peer reviewed global journals.

Despite our extensive background and experience, a review article should be critiqued on its content, not the eminence of its authors. A medical student is entitled to publish a manuscript. If the content is objective, accurate and informative, publication is appropriate. AJGP has recently published material written by medical students.
7) SURGERY FOR ADVANCED MELANOMA: We failed to mention surgery for melanoma spread

In our manuscript on “latest developments”, we included the key point that, “Melanoma spread to nodes or elsewhere can be managed with medication.”

It is unclear what the Thompson concern relates to. We at no stage suggested that surgery had no place in metastatic melanoma.

This manuscript was entitled, “Latest developments”. We focused on changes in the last ten years in melanoma research / practice that would be the most valuable to bring to the attention of Australian GPs. Ten years ago, there were no drug options demonstrated to improve survival for melanoma patients with metastatic melanoma.

By 2019 there were many clear important drug therapies available. The place of surgery is becoming less clear as the efficacy of drugs has become apparent.

Regarding surgery, it was important to note that we mentioned the changing role complete dissection of remaining nodes following a positive SLNB.

We did not consider that any other change in surgery for melanoma management in the past ten years warranted special attention in this word limited manuscript.
8) ULTRASOUND & FINE NEEDLE BIOPSY. We were wrong to advise that “Ultrasound and fine needle biopsy (US/FNB) can diagnose nodal metastatic disease as accurately as SLNB”.

Newer ultrasound methods (including the Berlin criteria, which is thus far the most accurate) are in fact common practice across many European centres including Spain, France, Netherlands, Romania, Estonia and Germany. Contrary to Prof Thompson’s suggestion, these units have found US to be an effective technique which can often result in many patients having no need for SLNB.

The landmark paper is the recently published work of Oude Ophuis et al. The study authors are a multinational team of researchers, and not the findings of a single Berlin dermatologist, as suggested by Prof. Thompson. The team includes leading melanoma clinicians / researchers in Germany, Netherlands and France.


BACKGROUND: US-FNAC is a common diagnostic tool in the work-up of many cancers. Results in melanoma were initially poor (sensitivity 20-40%). Introduction of the Berlin Morphology criteria has shown potential improvement up to 65-80% in selected patients. AIM: This cohort study evaluates the long-term survival outcome of melanoma patients undergoing Ultrasound (US) guided Fine Needle Aspiration Cytology (FNAC) prior to sentinel node biopsy (SNB) or direct lymphadenectomy. METHODS: Between 2001 and 2010 over 1000 consecutive melanoma patients prospectively underwent targeted US-FNAC prior to SNB. The Berlin US morphology criteria: peripheral perfusion (PP), loss of central echoes (LCE) and balloon shape (BS) were registered. FNAC was performed if any factor was present. All patients underwent SNB or lymphadenectomy in case of positive FNAC. RESULTS: Median follow-up was 61 months (IQR 40-95). SN positivity rate was 21%. Survival analyses demonstrated that patients with positive US-FNAC had poor survival. After adjustment for SN status and other known prognostic features, patients with positive US-FNAC (hazard ratio (HR) 1.80, 95% CI 1.10-2.96) had worse survival than patients with normal US (reference). Patients with suspicious US and negative FNAC (HR 1.13, 95% CI 0.71-1.78) had survival comparable to patients with normal US. CONCLUSIONS: The long-term US-FNAC results support this step-wise approach to melanoma patients. Patients with positive US-FNAC have a poor survival and can be spared a SNB. Patients with suspicious US and negative FNAC should undergo SNB to detect microscopic occult disease. Completely US-FNAC negative patients might only require follow-up and no SN staging at all.

Note that in this study, all patients had BOTH SLNB and Berlin criteria US-FNAC. The Kaplan-Meier graphs of the SLNB positive patients as well as the Berlin US_FNAC patients have been published, directly comparing the two techniques ability to predict melanoma survival. These were published in a separate manuscript by the same European team. Their paper found that SLNB status was similar to Berlin US and FNB in predicting long term melanoma survival. The Kaplan-Meier curves for the SLNB positive versus negative patients were not statistically different to the Kaplan-Meier curves for US/FNB positive versus negative patients.


PURPOSE: Sentinel node (SN) status is the most important prognostic factor for overall survival (OS) for patients with stage I/II melanoma, and the role of the SN procedure as a staging procedure has long been established. However, a less invasive procedure, such as ultrasound (US) -guided fine-needle aspiration cytology (FNAC), would be preferred. The aim of this study was to evaluate the accuracy of US-guided FNAC and compare the results with histology after SN surgery was performed in all patients. PATIENTS AND METHODS: Four hundred consecutive patients who underwent lymphoscintigraphy subsequently underwent a US examination before the SN procedure. When the US examination showed a suspicious or malignant pattern, patients underwent an FNAC. Median Breslow thickness was 1.8 mm; mean follow-up was 42 months (range, 4 to 82 months). We considered the US-guided FNAC positive if either US and/or FNAC were positive. If US was suggestive of abnormality, but FNAC was negative, the US-guided FNAC was considered negative. RESULTS: US-guided FNAC identified 51 (65%) of 79 SN metastases. Specificity was 99% (317 of 321), with a positive
The efficacy of ultrasound imaging has been consistently demonstrated in various studies. Published data from the European Multicenter Selective Lymphadenectomy Trial demonstrated that ultrasound can accurately identify sentinel lymph nodes (SNs) in patients with melanoma. The study showed that ultrasound findings could guide the management of melanoma patients, leading to the potential avoidance of unnecessary surgical procedures.

CONCLUSION: US-guided FNAC of SNs is highly accurate. Up to 62% of patients with SN-positive results in our institution could have been spared an SN procedure.

This European group has found that three criteria in ultrasound assessment of the nodal basin are independently predictive of melanoma survival:
- Loss of central echos
- Balloon shaping
- Peripheral perfusion

At the very least, the long-term prospective findings of this European team indicate that for many melanoma patients, there is a non-surgical alternative to SLNB that warrants patient discussion regarding the informed consent process for the patient's being offered SLNB. (Note that this European study abbreviates sentinel node biopsy as SNB rather than SLNB).

There have been numerous recent research publications on melanoma and nodal ultrasound. Appendix 1 lists those published this century.

**THE THOMPSON STUDY DATA**

Prof. Thompson has argued that ultrasound “doesn’t work,” only detecting 8% of nodal metastases. He cites his own data from the MSLT2 trial.

**OBJECTIVE:** To assess whether preoperative ultrasound (US) assessment of regional lymph nodes in patients who present with primary cutaneous melanoma provides accurate staging. **BACKGROUND:** It has been suggested that preoperative US could avoid the need for sentinel node (SN) biopsy, but in most single-institution reports, the sensitivity of preoperative US has been low. **METHODS:** Preoperative US data and SNB results were analyzed for patients enrolled at 20 centers participating in the screening phase of the second Multicenter Selective Lymphadenectomy Trial. Excised SNs were histopathologically assessed and considered positive if any melanoma was seen. **RESULTS:** SNs were identified and removed from 2859 patients who had preoperative US evaluation. Among those patients, 548 had SN metastases. US was positive (abnormal) in 87 patients (3.0%). Among SN-positive patients, 39 (7.1%) had an abnormal US. When analyzed by lymph node basin, 3302 basins were evaluated, and 38 were true positive (1.2%). By basin, the sensitivity of US was 6.6% (95% confidence interval: 4.6-8.7) and the specificity 98.0% (95% CI: 97.5-98.5). Median cross-sectional area of all SN metastases was 0.13 mm; in US true-positive nodes, it was 6.8 mm. US sensitivity increased with increasing Breslow thickness of the primary melanoma (0% for <=1 mm thickness, 11.9% for >4 mm thickness). US sensitivity was not significantly greater with higher trial center volume or with pre-US lymphoscintigraphy. **CONCLUSION:** In the MSLT-II screening phase population, SN tumor volume was usually too small to be reliably detected by US. For accurate nodal staging to guide the management of melanoma patients, US is not an effective substitute for SN biopsy.

The Thompson study did not incorporate Ultrasound guided fine needle biopsy, shown to be required to maximise efficacy of early nodal detection.


The ultrasound criteria used in the Thompson study to determine whether a node was abnormal were the following:
- Length to depth ratio < 1
• Hypoechoic centre
• Inability to identify a hilar vessel
• A focal rounded area of low echos with increased vascularity

Note that only one of these four criteria overlap with the validated Berlin criteria. The Thompson study did not incorporate balloon shaping or peripheral perfusion. This despite these criteria being known to the MSLT1 research team since 2010


The Thompson study merely confirms that usage of the non-validated ultrasound criteria will not reliably detect early melanoma nodal involvement.

There is another Thompson study noteworthy in this discussion.


Fine-needle biopsy (FNB) has been reported as a rapid, minimally invasive technique for the diagnosis of metastatic melanoma. The diagnostic accuracy of FNB was assessed in a consecutive series of 2,204 FNBs of clinically suspicious lesions from patients with previous primary melanomas treated at the Sydney Melanoma Unit, Sydney, Australia, between January 1992 and December 2002. The sensitivity and specificity of FNB were 96.3% and 98.9%, respectively. There were 5 false-positive cases (0.6%), which were verified as metastatic adenocarcinoma (3 cases) or reactive processes (organizing hematoma and chronic osteomyelitis, 1 each). False-negative diagnoses (6.7% of cases) were associated with a variety of clinicopathologic factors, including difficult-to-access anatomic sites (eg, high axilla or deep inguinal), small lesions, and lesional characteristics such as fibrosis, necrosis, or cystic change. FNB is a highly accurate, rapid, and cost-effective procedure for the diagnosis of metastatic melanoma and should be considered as the initial diagnostic procedure of choice in patients with melanoma with clinically suspected metastases.

Thompson and colleagues found that FNB was very accurate at detecting melanoma. As such, it is a loss as to why his ultrasound study did not include FNB in the methodology for nodal assessment. Voit has shown us that adding FNB to the validated US criteria is essential in maximizing early melanoma detection in nodes.
**DOES PROF THOMPSON BELIEVE ULTRASOUND HAS A USE OR NO USE?**

Professor Thompson published two studies of US in 2019 with conflicting assessments.

Thompson concludes in his 2019 study that, “For accurate nodal staging to guide the management of melanoma patients, US is not an effective substitute for SN biopsy.”


Prof. Thompson also published this manuscript in 2019 suggesting ultrasound has a role in some patients.


Prof. Thompson’s argues that US is “not effective”, yet it can be an alternative to SLNB for the frail and elderly. If it is “not effective” as a non-surgical alternative, why is it suggested for some patients?

If indeed it has some role, why advocate that this non-surgical alternative cannot be discussed with other melanoma patients as part of the informed consent process for SLNB? His conflicting positions cannot be reconciled.

In our current patient centred world of medicine, the patients lead the decision making. The doctor’s role is to advise on choices. If it is OK for elderly patients to be offered US, then of course it is an acceptable alternative for ALL melanoma patients.

**ULTRASOUND AND FINE NEEDLE BIOPSY REQUIRES TRAINING AND SKILLS**

Nodal assessment through US and fine needle biopsy requires considerable training and skill in the newer techniques, (as does any operation such as SLNB). One is required to recognise and identify the ultrasound features that have been shown to be most valuable in predicting early nodal involvement rather than use traditional non validated approaches.

It is most unclear why Prof. Thompson is not working hard to ensure his and other Australian melanoma units improve their US and FNB skills to meet the standards experienced in Europe.

**8a. We should have cited the key Annals of Surgery study by Thompson on Ultrasound.**

As outlined above, Prof Thompson ‘s study used non-validated US criteria to diagnose early nodal involvement. Fine needle biopsy was not part of the protocol.


As stated in the complaint letter, the Thompson study demonstrated only a 7.9% likelihood that positive SLNB patients would have had a previously abnormal ultrasound.

He uses his study to discredit the more recent and accurate ultrasound method, stating that it has not been successfully replicated. He consistently opines inaccurately and disingenuously that because his study’s ultrasound methods are inaccurate, that all techniques are inaccurate.

His team’s US accuracy rates are among the poorest reported in the world literature. An objective response to such a study would be for the researcher to ask, “What are we doing wrong?” Yet, Prof Thompson ignores ample published evidence of the greater accuracy of US, apparently suggesting that since his US results are poor, all the other published studies must be wrong. His misrepresentations of his own study results have been criticised.

Note that none of us who disagree with his interpretation have demanded that his study be retracted. Rather, we follow the concept of enhancing science through debate and discussion.

8b. That we were wrong to conclude that when performed by an experienced clinician, USFNB can be reliable in detecting early melanoma involvement.

This complaint is essentially the same complaint as in (8) above.
9) DRUGS

Objections about our summary adjunctive therapy for melanoma.

The readership for our two brief melanoma updates are GPs. A brief overview of the drugs available is all that is required. Given the word count and reference limitations, no drug doses or extensive detail regarding individual drugs or combinations of drugs was intended and was not required.

GPs need to know that there are drugs available for melanoma patients that may be beneficial and prolong life. Though GPs do not provide adjuvant drug therapy, they need to know which subgroups of melanoma patients should be considered for referral for drug therapy, the types of agents that medical oncologists will utilize, and some of their potential adverse events. Our manuscript was not intended for medical oncologists.

We provided such an overview for GPs in a short manuscript with very limited references allowed. The team of authors from Australia have been engaged in many aspects of general practice training throughout their professional careers. GPs are not interested in guidelines specific to every disease they may encounter. They are interested in advocating for their patients. GPs want to see that their patients are provided suitable options for care when referred to specialists.

The accepted manuscript was accepted after appropriate peer review and revision. See appendix 2 and 3.

Most of the comments in the Thompson letter (from melanoma surgeons and oncologists) reflect an inability to understand what is needed to inform GPs, and demonstrate how specialists can micro-dissect simplified and clear messages and make them utterly confusing for the GP.

Thompson criticizes our work for omitting “critical information” several times. Their suggested “critical information” inclusions were invariably too detailed for our reviews written for GPs. We detail below examples of how inappropriate some drug therapy comments were in the Thompson letter. We detail each complaint about our comments on drugs in our manuscripts. We then respond to each in turn.

We are concerned five of the authors of the Thompson letter have conflicts of interest regarding pharmaceutical companies. Prof Thompson, Prof Long, Prof. Menzies, Prof Kefford and Dr Carlino all disclose pharmaceutical interests on the Cancer Council Web site. (See Appendix 5). All five failed to declare these conflicts on their letter to AJGP. Our input is without conflicts of interest. It is inappropriate for conflicted doctors to hide their conflicts and attempt to influence drug education provided by truly independent experts.

Iplimumab

Complaint 1. The discussion of iplimumab and reference to the trial of iplimumab and DTIC versus DTIC reported by Robert et al (ref 1) omits critical information and misreports other important information. This dose of iplimumab, 10mg/kg, used by Robert et al. is neither approved nor used in Australia (noting that toxicity is associated with dose - Ascierto et al, Lancet Oncol 2017; 18: 611–22).

There are some 251 studies where iplimumab has been used as an intervention for melanoma. We chose a relevant reference for the broad statement that we made. We do not mention dosages for any drugs as these are NOT relevant to general practice.

Complaint 2. The combination with chemotherapy (DTIC) is neither approved nor clinically used in Australia. We do not suggest this combination is being used. DTIC was simply a preparation used as a potentially useful agent as a control in the quoted study, it appears that the manuscript was read in an over critical pedantic way by the Thompson group and not in the context of a short paragraph about this therapy.

Complaint 3. The authors fail to cite the other critical publication leading to the approval of iplimumab at the dose of 3mg/kg used in Australia (Hodi et al., N Engl J Med 2010; 363: 711–23). This citation is one of many that could have been chosen. This Hodi trial also used a rather ineffective but potentially useful preparation in the control group.
Complaint 4. Discussion of rates of grade 3-4 adverse events without precisely defining what this means clinically is not of value to the readership. While some grade 3 toxicities are very clinically relevant eg colitis, others such of an asymptomatic elevated lipase are of no clinical consequence. Moreover the authors fail to distinguish between treatment-related adverse events and overall rates of adverse events. A review of a topic such as this should explain this.

GPs understand the grading of drug therapy adverse events and indeed these are listed in Table 1. GPs are familiar with major drug trials especially those of the drugs they commonly prescribe. They are also well aware that drug trials report all adverse events, and that not all are directly related to the drug involved. Adjudication of events and comparisons with placebo allows for the unexpected events that are drug related to be evaluated. Unfortunately, many of the pivotal studies have not looked at the active drug and placebo. Making the motherhood statements above are demeaning and belittling of GPs. This was not a systematic review of just one therapy.

In the manuscript, we did identify and explain each level of adverse events (AEs) for reader information

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

Prof. John Dixon finds it extraordinary (as a full-time researcher with extensive drug trial experience) to suggest that Grade 3 and 4 events may be of no clinical consequence. GPs know that at levels 3 and 4 they are by definition of clinical consequence. Unfortunately, the tendency to use drug-to-drug comparisons makes it difficult to readily assess specific drug related AEs.

Complaint 5. Table 1 reports the grade 3-4 adverse event rate from ipilimumab to be 46% or 56% at the non-approved dose of 10mg/kg, as reported in references 1 and 16. The rate of 56% is for the combination of ipilimumab and DTIC, not ipilimumab alone.

This is correct. Ipilimumab was the tested in combination with DTIC, with the control being DTIC. It is also clear that the combination generated higher levels of hepatic dysfunction and immune related events than DTIC alone.

Complaint 6. The grade 3-4 adverse event rate as reported by Hodi et al., at the approved dose of 3mg/kg, is in fact 23% for treatment-related grade 3-4 adverse events and 46% for overall grade 3-4 adverse events.

It is agreed there are a high rate of grade 3 and 4 events in these trials. GPs can expect these in their patients. Again, interpreting adverse events is difficult if no placebo group is included. The placebo controlled Eggermont et al. study (N Engl J Med 2016; 375:1845-1855) shows in Table 3 from study that Immune related events are far more common than in the placebo group.

![Table 3. Immune-Related Adverse Events.](image-url)

The safety analysis included all the patients who underwent randomization and received at least one dose of ipilimumab or placebo (945 patients). Immune-related adverse events that occurred in at least 10% of the patients are reported. Patients may have had more than one event. In the ipilimumab group, 5 patients died because of drug-related adverse events; 3 patients died from colitis (2 patients with gastrointestinal perforation), 1 from myocarditis, and 1 from multiorgan failure associated with the Guillain-Barre syndrome.

**Gastrointestinal perforation occurred in seven patients (1.5%) in the ipilimumab group (all such events were considered to be related to ipilimumab) and in three patients (0.6%) in the placebo group (none of these events were considered to be related to placebo).**

1. In the ipilimumab group, 26 patients had a grade 3 or 4 (death) event. 4 had a grade 3 or 4 immune-related event (hypersensitivity, autoimmune disorder, anaphylactic reaction, or drug hypersensitivity), 4 had grade 3 lung infiltration, pneumonitis, or interstitial lung disease, 1 had arthritis, and 1 had uveitis.
BRAF / MEK

Complaint 1. The discussion of BRAF inhibitors and MEK inhibitors also makes incorrect statements and omits critical information.

The comments at the start of the drug section of this communication are again appropriate. The audience are GPs. The BRAF / MEK drugs Dabrafenib and Vemurafenib are reported in 73 and 108 interventional studies respectively up to 2018. For an overview, the information we provided is all that is needed. We did not omit any information critical for this audience. The more complex the information provided the fewer key messages that are retained.

Complaint 2. The discussion of toxicity profile under the subheading “combines toxicities from both vemurafenib (refs 4 and 7) and dabrafenib (refs 5 and 8). The statement ‘The adverse event profile is similar for both BRAF inhibitors’ is incorrect. There are substantial differences in the toxicity of these agents, most notably photosensitivity 52% for vemurafenib (Sosman et al. N Engl J Med 2012;366:707-14) and 3% for However (Hauschild et al., Lancet 2012; 380: 358–65); and fever 28% for dabrafenib, 22% for vemurafenib, 57% for dabrafenib and trametinib (Long et al., N Engl J Med 2014;371:1877-88) and 26% for vemurafenib and cobimetinib (Larkin et al., Engl J Med 2014;371:1867–1876).

Selecting individual adverse events to highlight differences between therapies is prone to selection bias. Roche is the manufacturer of vemurafenib and Thompson does not appear to have a conflict of interest (COI) with them. (See appendix 5). However, Thompson does have conflicts with Novartis and therefore a potential bias toward dabrafenib. By selecting adverse events less common in this drug is evidence of bias or at least perceived bias and COI should have been declared in the letter to AJGP.

It is clear that these two drugs have different AE profiles, and that the AE rates reported from study to study vary enormously. An exhaustive review of differences in AE profiles is inappropriate and confusing for the GP/primary care audience.

Complaint 3. The section on MEK-inhibitors omits any reference to the other approved BRAF and MEK inhibitor combinations in Australia - vemurafenib and cobimetinib, and encorafenib and binimetinib.

No attempt was made to provide any details beyond examples. To do so would be inappropriate for GPs.

Complaint 4. Table 1 misreports the rates of grade 3-4 adverse events for BRAF+MEK inhibitors (dabrafenib and trametinib). Table 1 states these are 8% and 15% for dabrafenib and trametinib in two trials (refs 12 and 29 respectively). In fact, the grade 3-4 adverse events as reported in reference 29 exceeded 50% in all 4 cohorts and grade 3-4 events exceeded 40% in all larger phase 3 trials (Long et al., N Engl J Med 2014;371:1877-88 and Robert et al., N Engl J Med 2015;372:30–39).

The text correctly identifies and cites the efficacy and AE of combination BRAF & MEK drugs in general. The rates of AE for specific drug combinations would not have been possible due to word count and reference limitations and are of no interest or relevance to GPs.

Complaint 5. The discussion of ‘nodal’ involvement in this section is confusing to the reader as all the clinical trials referred to in point 1 above relate to metastatic melanoma, that is, unresectable stage III and IV disease, which included some patients with unresectable nodal disease. The clinical trial presented in this section evaluated dabrafenib and trametinib in the adjuvant setting following surgery and included some patients who had microscopic nodal involvement identified by sentinel lymph node biopsy. This, coupled with the lack of any reference to the AJCC staging system, used to determine trial eligibility, is a significant omission.

We have addressed these concerns above in sections 1, 3 and 4.

Anti-PD-1 medications

Complaint 1. The discussion of PD-1 inhibitors again makes incorrect statements and omits critical information. This section discussing pembrolizumab again confuses nodal involvement that is unresectable in the advanced setting from microscopic nodal involvement in the adjuvant setting, with no clear delineation between them. We have addressed these concerns in sections 1, and 4 above. Note that pembrolizumab was not and is not yet indicated for microscopic nodal involvement in the absence of subsequent complete node excision.
**Complaint 2.** In the nivolumab section reference is made to the relapse-free survival for pembrolizumab not nivolumab. This complaint is valid. We inadvertently referred to nivolumab when the other PD-1 drug pembrolizumab was intended. This therapy had been mentioned in the previous paragraph. An accidental error that should have been picked up during the author, review or production process. Nevertheless, the two drugs are of the same class. The inadvertent error has no effect on the conclusions of the manuscript.

**Complaint 3.** Table 1 again misreports the rates of grade 3-4 adverse events by failing to distinguish between treatment-related adverse events and overall adverse events. In the referenced studies these are 14% and 23% respectively for nivolumab and 15% and 32% respectively for pembrolizumab. Ref 15. This correctly quotes trial drug-related adverse events as 15% for pembrolizumab. **“Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 14.7% of patients in the pembrolizumab group and in 3.4% in the placebo group. There was one pembrolizumab-related death due to myositis”**. Ref 16. This correctly quotes trial drug related adverse events as 14% for nivolumab. **“Grade 3 or 4 adverse events that investigators deemed to be related to a trial drug were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group”**. This issue of related and unrelated adverse events has been discussed above.

**Complaint 4.** The section on combination immune checkpoint therapy fails to cite the most recent survival data (Hodi et al., Lancet Oncol 2018; 19: 1480–92). This is highly relevant, given incorrect statements made on page 352 about long-term outcomes. The Hodi findings are consistent with the summary we provided. Citing this study’s results would not have changed the comment made in our manuscript. Our manuscript states: The survival benefit of these drugs offers added months and potentially added years for patients with melanoma. This is precisely what this additional Hodi study shows.

**Complaint 5.** The authors state that eligibility for the EORTC adjuvant study (pembrolizumab vs placebo) required lymph node clearance in response to a positive sentinel node biopsy, yet they neglect to mention that the CheckMate-238 trial (nivolumab vs ipilimumab) also required this (Weber J et al N Engl J Med. 2017;377(19):1824-35). This appears to reflect defense of vested interests. Both trials required lymph node clearance, and, again, this added detail would be of very little relevance for a GP update.
Controversy

Complaint 1. The authors neglect to state that lymph node clearance was the accepted standard care at the time the trial was conducted (pre MSLT-II publication) and omits the critically important information that the current Australian approval, based on the results of MSLT-II, does not require lymph node clearance for patients to access adjuvant therapy and that lymph node clearance is not required for subsequent (NCT03068455) and ongoing adjuvant clinical trials.

We refer to (1) above. Current Australian TGA approvals REQUIRE complete node resection for patients to access melanoma drugs. Any other usage outside of the trial setting is “off label”.

Non-TGA approved protocols can be used in the drug trial scenario subject to ethics committee approval. It is good to see the MSLT-II publication has made sensible changes such that some new drug trials do not require complete nodal resection. We emphasise the need to respect the MSLT-II results in our manuscripts. We also emphasise drug protocols that are TGA approved. We do not mention “off label” usages.

Complaint 2. The authors’ statement that sentinel node biopsy (SNB) is required to identify patients for clinical trials that may offer survival benefit is no longer relevant, given there are now three TGA-approved adjuvant therapies for patients with resected stage III melanoma, all of which have proven survival benefit.

We are confused by this criticism. Patients with stage III melanoma are defined as having nodal metastases. Nodal metastases can be identified by fine needle biopsy, SLNB or complete lymph node basin resection. Patients who are clinically negative for nodal disease require pathology evidence of nodal diseases and if positive, nodal basin clearance to be eligible for life prolonging adjuvant therapy. As the Thompson group only support SLNB, they will require this for identifying nodal disease in these patients. We disagree that this is the only test that can identify subclinical nodal disease.

Our manuscript clearly states adjuvant therapies for established nodal disease prolong life. We specifically state, “Drugs are available that prolong survival in patients with metastatic melanoma including nodal spread”.

Complaint 3. Furthermore, it is incorrect to state that use of medications be “erroneously restricted to patients having positive nodes detected by SNB” as all adjuvant trials of medical therapy have also included patients with metastatic disease detected clinically or by imaging.

Our concern here is the apparent neglect of high-risk melanoma patients who are node negative. This is best explained through two examples.

Patient “A” has a Breslow 3 mm ulcerated primary tumour on her back. A SLNB is performed and is negative. This patient has a 5-year survival prospect of less than 75%.

Patient “B” has a Breslow 1 mm non ulcerated tumour on her left leg. A SLNB is performed and is positive. Patient “B” has a more favorable outlook than patient “A:” with a 5-year survival prospect greater than 85%.

As it stands, patient “A” will not be recommended for adjuvant therapy, as existing published trials excluded patients in this risk category. In contrast, Patient “B” will be offered complete nodal dissection and then drug therapy. Patient “A” is being erroneously restricted to adjuvant therapy.

Complaint 4. Importantly, the authors fail to indicate the critical point that for patients who are clinically node negative the ONLY method for patients to be eligible for these efficacious treatments would be the identification and removal of micrometastatic nodal disease via a sentinel node biopsy (as this defines a higher risk group where adjuvant treatment has the greatest proven benefit).

This complaint reinforces our concerns regarding complaint (3) above. Also, complaint 4 contradicts the statement above where Thompson acknowledges that imaging may identify involved subclinical nodes. Clearly any method that can identify subclinical disease can enable patients with nodal involvement to be treated. Regardless of the method of diagnosing nodal involvement, subsequent complete node resection is still required under current TGA approvals in order to access adjunct drug therapy.

Long Term Benefit

Complaint 1 The discussion of long term benefit includes further incorrect statements and once more omits critical information. The authors fail to acknowledge and omit the critical information that many patients with metastatic melanoma treated with systemic therapy have an excellent prognosis. As an example, analysis of the Keynote-006 study found that with single agent pembrolizumab treatment in patients who obtain a complete response, 2 year progression-free survival was 91% (Robert C et al, J Clin Oncol. 2018)
Our summary was accurate. Only 16% had a complete response. This is NOT an excellent prognosis with this therapy. This data reflects a highly selected subgroup. Median overall survival in all 655 treated patients was 23.8 months (95% CI, 20.2-30.4), with 3-year and 4-year survival estimates of 42% and 37%, respectively. Unfortunately, this statement from the Thompson letter misrepresents the study. Of the 665 participants 90% of 67 patients who discontinued pembrolizumab after CR for observation were estimated to be disease free at 24 months.

Results of clinical trials look at intention to treat results. It is entirely inappropriate to promote a drug’s efficacy based on responder response. What happens to responders is interesting for predicting outcomes and for the responders.

This study was not a clinical trial and had no comparator group. Of those initiated on Pembrolizumab, 104 (15.9%) were still receiving treatment as of the data cutoff date; median follow-up was 43 months (range, 36 to 57 months). The most common reasons for treatment discontinuation were progressive disease (41.7%) and adverse events (25.0%). Median duration of pembrolizumab exposure was 6 months (range, 1 day to 55 months). Robert C et al, J Clin Oncol. 2018. Yes, it appears better than expected but a 10% - 10 year survival is seen in untreated individuals yet fails to have a contemporary control group.

To have indicated that this drug allowed for an excellent prognosis is grossly misleading and it would have been irresponsible to quote Thompson’s suggested data in our manuscript. The only conclusion from this manuscript that could be sustained is that those that responded better tended to live longer.


The above statement from the Thompson letter is grossly misleading as a complete response occurred in only 109 patients (19%) and was associated with an improved long-term outcome, with an overall survival rate of 71% (95% CI, 62 to 79) at 5 years. Unfortunately, the overall survival rates of the entire study population were 37% at 4 years and 34% at 5 years. However, the progression-free survival rates were 21% at 4 years and 19% at 5 years. In essence 1/3 survived 5 years and of those 44% had evidence of progressive disease.

This study combines the 2 treatment groups from 2 trials and does not look at the control groups. Its focus appears to be primarily on examining predictors of response. Those that responded, did best, other biomarkers were not able to predict disease free status following drug cessation. There is no discussion regarding excellent prognosis.


In drug trials the primary outcome is related to intention to treat, responder analysis tries to identify characteristics of those more likely to respond, and for those who respond provided a secondary outcome measure.

It is implausible that GPs would interpret these drugs as generating an excellent prognosis.

Complaint 2. The statement that “Many patients choose to withdraw from therapies because of intolerance of adverse events” is incorrect. In fact, the rates of discontinuation are low – less than 15% for BRAF-targeted therapy (ref 9) and less than 12% for anti-PD-1 monotherapy (ref 14)

Reference 9 (BRAF therapy). The rates of permanent treatment discontinuation because of adverse events were similar (13% and 12%, respectively). Adverse events leading to dose reduction were reported in 33% of patients in the combination-therapy group and 39% of those in the vemurafenib group; adverse events leading to dose interruption occurred in 55% and 56%, respectively. This reference indicates that more than 90% of AE were considered related to the interventions. In addition to the total cessation of therapy, many has dosage reductions or interruptions to therapy. In summary: Adverse events were common and interfered in a major way with the intended intervention protocol.

Reference 14 (Pembrolizumab). The rate of discontinuation for anti-PD1 was 7% and 11% in the 2 different pembrolizumab arms (ref 14), so it was in fact low by comparison with BRAF studies. This is shown in the table below. This can be contextualized using the rate of discontinuation in the placebo arm in the study comparing pembrolizumab vs placebo in the adjuvant setting, which was 2.2% (ref 15 and Eggermont et al AACR 2018).
However, in a phase 1 study: pembrolizumab, 104 subjects (15.9%) were still receiving treatment as of the data cutoff date; median follow-up was 43 months (range, 36 to 57 months). The most common reasons for treatment discontinuation were progressive disease (41.7%) and adverse events (AEs; 25.0%). Median duration of pembrolizumab exposure was 6 months (range, 1 day to 55 months). KEYNOTE-001 study (ClinicalTrials.gov identifier: NCT01295827).

In a Phase 3 trial, of the 509 patients who started pembrolizumab, 70 (13.8%) discontinued the regimen owing to an adverse event; in 66 patients (13.0%), the event was considered by the investigators to be drug-related. Among the 502 patients who received placebo, 11 (2.2%) discontinued the regimen owing to an adverse event; in 8 patients (1.6%) Robert C, Ribas A, Hamid O, et al. Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma. Journal of Clinical Oncology. 2018;36(17):1668-1674.

Substantially more stopped therapy in the actively treated group compared with the placebo group. The rate of discontinuation in the first phase 3 trial of dabrafenib and trametinib vs dabrafenib in metastatic melanoma was only 9% in the combination arm (Long GV NEJM 2014), and 13% in the phase 3 trial following it (ref 9). Discontinuation rates were 9% in combination arm, however 25% required dosage reductions and 49% had interruptions to treatment due to adverse events. (Long GV NEJM 2014)

Adverse events were common and interfered in a major way with the intended intervention protocol. The manuscripts were written for a GP audience. Compared to the majority of medications that GPs prescribe for their patients, this order of drug cessation due to adverse events can reasonably be described as “many”.

**SUMMARY**

The complaint letter from Thompson and others fails to identify any error of substance in either of our two accepted and published manuscripts. There were minor errors in the drugs section of “Latest Developments,” which we agree, in correspondence to the Editor, could be addressed by publication of a Corrigendum. None of these minor errors alter the key points and context of outlining for GPs a summary of the new drugs available and when they can be used.

Inclusion of the purported omissions Thompson cites would have been inappropriate for the target audience and impossible given word count and reference limitations.
It is clear that there are many differences of opinion regarding our paper that are mentioned in the Thompson letter. None are errors of fact. In particular, whether or not the CGN melanoma guidelines are suitably evidence based is a difference of opinion. It is certainly no basis for retraction under COPE guidelines. Standard scientific practice is for the AJGP editor to offer a place for the Cancer Council and others to express their different opinions through a letter published in the AJGP.

The request for manuscript retraction was inappropriate and groundless. It appears to be an act of intimidation because Prof Thompson and his colleagues saw information from other academics that differed from theirs. Thompson’s letter contains many personal attacks rather than scientific argument. This is a form of bullying and is not acceptable in the scientific medical community.

In January 2020 we were provided with the alleged reviews that we were advised all concurred that retraction was needed. (Appendix 4). **Note that only one reviewer of three suggested retraction.** Note also that these reviews are little more than personal abuse and insults thrown at our research team. No error in our manuscripts was identified in these reviews.

Simply, no legitimate case for retraction of our articles has been presented. Retracting researchers’ articles has serious implications for a researcher. It casts doubt on all aspects of the researcher’s output and published reports. This is one reason that retraction is a last resort for a journal. In this case it is clear that differences of opinion could have been addressed appropriately through letters to the editor from those concerned.

Retraction should never have been requested.

The interference by Thompson et al, on our adjunctive therapy education raises many concerns

1. None of the authors of the letter declared conflicts of interest with the pharmaceutical companies providing therapies. It is known that five have such conflicts. (Appendix 5).
2. There is bias in the selection references that were not quoted in our manuscripts.
3. There is inappropriate selection of specific adverse events to promote one drug in a class with another.
4. Bias is demonstrated in discussion of the melanoma drugs’ adverse events rates reported in the literature.
5. The authors downplay the clinical relevance of Grade 3-4 events.
6. The authors are downplaying the effects of adverse events on interfering with intended drug protocols.
7. Gross misrepresentation of the outcomes of drug therapy. The suggestions of excellent prognosis show gross bias and are totally inappropriate.

These concerns indicate bias regarding the safety and efficacy of drug therapies for treating advanced melanoma. They represent vested interests of pharmaceutical companies, the authors’ institutions, and their own individual practices. These issues are beyond simply the retraction of our manuscripts.

This attempt to manipulate independent information provided by experts with no conflicts of interest requires investigation. It is little wonder the authors of this letter to the editor to the editor refused to cooperate with the editor in chief of the Journal to provide an acceptable version considered suitable for publication.
CONCLUSION

1. There is no case for retraction of our manuscripts.  
   - The manuscripts must be reinstated immediately.
2. The objections against our manuscripts are biased and stated by many with undeclared conflicts of interests.  
   - An investigation into this improper interference is necessary.
3. The authors of our manuscripts require an apology.

Kind regards,
Dr Alexander Nirenberg  
Prof Anthony Dixon  
A Prof Howard Steinman
Prof John Dixon  
Dr Stuart Anderson
APPENDIX 1 – PUBLISHED MANUSCRIPTS ON US/ FN

References since 2000 on ultrasound usage detecting nodal involvement in melanoma patients. These are all available on Pubmed.

Dear Dr Dixon,

Manuscript ID AJGP-01-19-4825, titled 'Invasive Melanoma Management', which you submitted to The Australian Journal of General Practice, has been reviewed. The comments of the reviewers are included at the bottom of this letter.

The reviewers have suggested some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewers' comments and revise your manuscript. Your revised manuscript will be subject to editorial review and may also undergo repeat peer review.

The Australian Journal of General Practice
stephen.margolis@racgp.org.au

Reviewers' comments to author:

Reviewer: 1
Comments to the Author
A good article giving practical advice and guidelines in the management of primary melanoma. Have you considered including the use of dermoscopy for identifying clinical margins prior to excisional biopsy and for identifying the most concerning areas when faced with a large clinically suspicious lesion that requires biopsy and excisional biopsy is not possible.

Reviewer: 2
Comments to the Author
I have concerns about some of the assertions made in this manuscript. I'm not sure suboptimal aspects of melanoma management have been addressed apart from the pitfalls of partial biopsy and there are errors in some of the papers quoted?

ABSTRACT: "many melanoma patients are not managed ideally" - please reference and/or expand.

INTRO
Circumstances for referral for systemic therapy have not been addressed satisfactorily.

BIOPSY TECHNIQUE
Partial biopsy is not synonymous with incisional biopsy. What is a "thick" shave biopsy? Preferable term is saucerisation biopsy perhaps? The Ng study has been misquoted. False negative diagnosis with shave biopsy was OR of 2.7 (p 0.02) not 2.6 as stated and relative risk increase for punch biopsy was 14.7 not 1.7?

RISK FACTORS
In the paper referenced (7) it should be stated that these figures pertain to intermediate thickness melanoma that has undergone SLNB. This actually showed that SLNB status was a more powerful predictor of prognosis than Breslow thickness.

MARGINS
Please expand on "poorly differentiated" melanoma perhaps with a reference? The recent guidelines referred to are not the 'ANZ guidelines' - rather they are the Cancer Council of Australia Clinical Guidelines Network for melanoma (wiki platform). This should be referenced correctly to the website.

Confocal microscopy has been neglected in the assessment of MIS, only Woods lamp rates a mention. Dermoscopy deserves a mention here too.

Note ref 4 is 12 years old. More recent references preferred.

When is SLNB required?

"A SLNB is not required in the management of any melanoma" is far too simplistic and unqualified especially as it remains a valuable prognostic or staging tool that is widely used in expert melanoma MDT clinics. The 2nd last sentence/assertion really needs expanding/qualification. I find this paragraph too brief for an overview of suboptimal management.

INVESTIGATIONS
The assertion that early imaging is of uncertain benefit is a 15 yr old reference. Please see Lewin J et al Annals Oncol July 2018 as one more recent positive study on the benefit of imaging surveillance at least in high risk stage 3 patients.

The statement that early detection of secondaries may not alter efficacy of newer treatments is against contemporary
oncology opinion too.

DRUG THERAPIES
MEK inhibitors and CTLA-4 antagonists neglected.
Really too simplistic paragraph

FOLLOW UP
Too didactic as some studies demonstrate the FU intervals are a bit arbitrary. Note that melanoma units do not usually take on follow up of primary melanoma rather stage 3 and 4 only.

CONCLUSION
SLNB statement too concrete/controversial as it is a valuable staging/prognostic tool.

REFERENCES
First mention of ref 20 incorrect? WRT investigations whilst ref 20 was a sunscreen RCT. Ref 20 has not been cited correctly either.

KEY POINTS
Point 3 really has been addressed lightly

Reviewer: 3
Comments to the Author
Basically a well and succinct written review article. Obviously the statement on sentinel lymph node biopsy is not in accordance with the actual Australian Melanoma Guidelines. In the spirit of transparency this should be made crystal-clear and the current guideline statement should be cited --
https://wiki.cancer.org.au/australia/Clinical_question:When_is_a_sentinel_node_biopsy_indicated%

Additional comments:
@ Australian and NZ Melanoma Guidelines -- the guideline from 2008 is indeed Australia and New Zealand -- the recent Wiki Guidelines are Australia only
@ ...with a 5mm margin of clearance -- please clarify that clinical margin is meant
@ the wood light statement is a dated ones -- ref from 1988 -- the reviewer knows that in a few clinics in Victoria this practice is still ongoing -- worldwide it is not done!
@ As mentioned above the sentinel node biopsy statement is not in accordance with the current approved Australian guidelines and this needs to be stated in the spirit of open communication
@ histopathology instead of histology throughout the manuscript
@ Closure of defect technique -- or instead of

The manuscript was subsequently revised in keeping with reviewer comments, accepted and published.
Dear Dr Dixon,

Manuscript ID AJGP-01-19-4824, titled 'Cutaneous melanoma latest developments', which you submitted to The Australian Journal of General Practice, has been reviewed. The comments of the reviewers are included at the bottom of this letter.

The reviewers have suggested some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewers' comments and revise your manuscript. Your revised manuscript will be subject to editorial review and may also undergo repeat peer review.

(Standard paragraphs on process of amending and resubmitting).

Sincerely,
Prof Stephen Margolis OAM
Editor in Chief
The Australian Journal of General Practice
stephen.margolis@racgp.org.au

Reviewers' comments to author:

**Reviewer: 1**
Comments to the Author
I thought the section dealing with the latest Immunotherapy options for metastatic melanoma was helpful for the GP readership. However I felt the SLNB discussion was confusing and although your opinion regarding the usefulness of this procedure is important it would be better if you included this in the discussion section of your paper.

**Reviewer: 2**
Comments to the Author
Very detailed explanation of current treatment regimens for melanoma. BRAF and MEK inhibitors perhaps need defining.

**Reviewer: 3**
Comments to the Author
Well researched and up to date information on the management of melanoma. I found it a very interesting read and have learnt a few points from the article. Highly relevant to GP and sharing care with Melanoma units in tertiary hospitals.

The manuscript was subsequently revised in keeping with reviewer comments, accepted and published.
APPENDIX 4 – The reviews following the Thompson letter and our point by point reply

Text in black is text provided by the AJGP reviewers
Text in red is text provided by manuscript authors
The comments section is also provided by manuscript authors

Reviewer A

Overall summary

For me the big issues are:
1. The team assembled by Dixon et al does not on the face of it seem to have the needed breadth and depth of expertise to cover the topic. The absence of an oncologist or a melanoma surgeon or as far as I can tell any practitioner working on a daily basis with advanced melanoma is to me a major failing. Relevant clinical experience informs the interpretation of data. See comment A
2. Serious concerns have been raised by a broad array of eminent and respected Australian practitioners who represent high level expertise across all facets of melanoma management. See comment B
3. Dixon et al clearly reject almost all these concerns. It will likely be impossible to resolve these issues. 4. Ultimately all involved would want the readership to have access to a well written, cogent, concise, evidence based and practical overview of this important issue. See comment C
I think allowing the pages of your journal to be used for what will inevitably become an ongoing 'to and fro' of responses and rebuttals is no solution. See comment C

Detailed assessment across all three papers

As you would be aware sentinel node biopsy has long been a subject of controversy and very heated debate. It is one of those topics that attracts some to take what can only be described as a partisan approach.

The advent of the new treatments for melanoma has seen an incredible change in patient outcomes. However, there is still considerable work being done on the optimal utilisation of our available agents.

I have tried to look at this issue from the viewpoint of the readership of the journal. See comment C
Dixon et al have written a paper on Melanoma. The authors assembled for the paper are unusual in that they do not appear to be recognised experts in this subspecialty field. See comment A
I would note there does not appear to be an oncologist included for instance. To me this is a major failing especially when so much of the article is devoted to treatments delivered by oncologists. For a review article such as this you would reasonably expect an author actively involved in the use of these agents. I might be wrong but from what I can read of their CVs none of the authors would be able to lay claim to this level of experience. That does not prevent them from having an opinion but if I was setting out to write such an article, I would be deferring to doctors practicing in the field. See comment A

Then you have the authorship of the letter of concern. (redacted sentence) A brief perusal of their affiliations show that many are working/running tertiary referral centres involved in high level care of advanced melanoma. They represent a truly multidisciplinary array of expertise in this area. In short, their opinions carry weight. See comment B

The objections they raise are cogent and supported by reasoned argument and references. See comment D

Then we read Dixon et al response I suspect we run the risk of entering into a protracted and ultimately unrewarding and indeed confusing for the readership, 'debate'.
In fact I doubt that any but a small minority of your readership would want to read the inevitable 'to and fro' that this situation is likely to generate. See comment C
Dixon et al raise a semantic issue re the cancer council guidelines as to whether they are published or not. I take their point but these guidelines are a valuable reference for Australian doctors including I would suspect all your readership.

In many instances where the 'letter of concern' has pointed out what they believe to be errors the Dixon et al response has been "We believe we were accurate and correct." or some similar phraseology. For a reader it is quite likely this will
then be seen as a 'he said, she said' argument and they will emerge confused. No amount of measured debate, use of references etc will clarify this and in any event I doubt many doctors would read through it. See comment D

The ad hominem aspersions that some of the authors of the letter of concern are acting as agents of pharmaceutical companies is regrettable. See comment E

This has the potential to become a vehicle for ongoing rancour, claims of big pharma interference in scientific publications etc and at the same time produce no useful outcome. See comment C

Additional summary specifically regarding Dixon rebuttal of Thompson letter See comment F

Redacted see comment F

These are their recommendations (recommendations of a group that doesn't have much experience in treating melanoma) See comment A. Redacted see comment F

Additional detail regarding Dixon rebuttal of Thompson letter See comment F

Redacted see comment F

I would like to know the credentials of these authors and the amount of melanoma work they have published to be able to put these comments into context. See comment A

Page 4 "One of the contributors to the draft section on SNLB in the CCACGN withdrew his support because the draft did not provide a balanced viewpoint." No reference? No personal communication? No names? This is very inappropriate in a journal. This is fact. The contributor that withdrew his support because the SLNB section was not balanced was Assoc. Prof Mike Sladden, University of Tasmania. These are the exact words used by Dr. Sladden. This lack of endorsement would be well known to Prof Thompson et al.

Redacted see comment F

"Completion lymphadenectomy does not improve survival in patients with subclinical nodal disease. Patients should not be required to undergo such unnecessary nodal surgery to qualify for adjuvant drug therapy." The authors confuse CL with SLNB. We cited the MSLT 2 study. In this study, patients with a positive SLNB were randomized into completion lymphadenectomy versus observation. We correctly cited the study conclusion that CL does not improve survival. It seems here that the reviewer is confusing CL with SLNB.

Redacted see comment F
Reviewer B

Overall summary

The first two articles contain too many errors to be considered useful synopses of the topic. (No errors actually specified.) This third article is an attempt to rectify that but that is not possible in this format. See comment F.

The readership will be left confused. I suspect the first two articles contain so many errors they should be withdrawn. That would make this article redundant. See comment F

Detailed assessment across all three papers

There are very strong personalities with very defined and opposite opinions regarding SLNB, but, in other topics, Dixon et al have shown a poor understanding of the melanoma field. Is the reviewer referring to material outside of manuscripts A and B.? No errors specified nor justification of the poor understanding comment is offered. See comment D

and the letter of response to concerns shows a lack of insight. See comment F

Certainly, it is difficult to discuss the value of the team that has signed the letter of concern (Thompson et al). The amount of knowledge, papers, and citations of the melanoma group is overwhelming and comes from Sydney, Melbourne and Brisbane, including the Australasian College of Dermatologists and the Cancer Council, J Thompson: https://scholar.google.com.au/citations?user=_WDGp94AAAAJ&hl=en G Long: https://scholar.google.com.au/citations?user=Ec4KfDMAAAJ&hl=en R Scolyer: https://scholar.google.com.au/citations?user=wXXa_RIAAAAJ&hl=en etc... See comment B.

On the other hand,
John Dixon has a great CV, but related to diabetes, obesity... There are no papers about melanoma in his 200 most cited papers.
A Pubmed search does not give much in relation to melanoma knowledge. See comment A.

As I said before, the authors do not manage melanoma patients on daily basis, nor the medications. See comment A.

**** “As I said before, . . .” Not exactly. The only person to make this comment before was reviewer A. Are reviewer A and B the same person? ****

In the first paper, the section about “Controversy” is poor. Although trials were designed with a requirement for SLNB, drug companies are changing their requirements for new trials. Drug companies are changing protocols so as SLNB and CL is not necessarily required. Whilst new trials are using new protocols, the published trials we cited were designed exactly as we described. All TGA approved protocols are based on published data.

Dixon et al, that do not participate in trials, are unaware of this. See comment A. In fact, our team has designed, effected and published many randomized controlled drug trials.

Dixon et al do not know how pharmaceutical companies design their studies to achieve defined outcomes. See comment A. We are well experienced in pharmaceutical company sponsored studies. Further, our team has designed, effected, completed and published a randomized controlled drug trial with no sponsorship or involvement of drug companies.


We are well aware of the influence pharmaceutical companies play in trial processes. We are also well aware of how different it is when such companies are not involved.
The sections about “long-term benefit” or “second primary melanoma” with statements such as “Whether there is a five-year or 10-year survival benefit from these medications, including combinations, remains unknown” or “patients with melanoma who develop a second cutaneous primary melanoma who are not offered surgery for the new melanoma because they are on one or more of the medications listed previously” shows again a lack of knowledge and a extreme bias. See comment G

5-year survival for antimalanoma therapies have been reported in congresses for a few years and published recently. See comment H Redacted see comment F).

Anecdotes about patients not being offered surgery requires appropriate source, otherwise is misleading. No melanoma doctor will leave a second primary “because they are on one or more of the medications”. This is unacceptable. See comment G

The second paper has less issues of concern. That the authors do not know about the Cancer Council guidelines is surprising, but in keeping with their lack involvement in melanoma management and limited literature review. We comment on the cancer council guidelines. We could not have done so if we did not know of them. They do not comment on sequential digital dermoscopy. Our two manuscripts for the June edition of AJGP were two of six commissioned for that edition on skin lesions. We were advised that another author had been invited to update GPs on dermoscopy, and hence were advised to leave this topic out of our manuscripts. They do not discuss that wide local excision should be performed at the same time as SLNB if this is performed. See comment I.

Making the comment that FNA can reliable detect early nodal involvement shows the lack of knowledge of basic biology. If the analysis of a whole lymph node may only detect small depositions, an FNA will be less reliable. If the diagnosis of these lesions has an impact in prognosis is another topic. See comment J.

Redacted see comment F

That Dixon et al consider that the authors of their papers are as good as the authors of the Cancer Council Guidelines shows a deep lack of insight, and lack of respect. The Guidelines are published online with adequate summaries and recommendation supported by literature. The comments from Dixon et al show a deep lack of understanding, and a poor justification for their ignorance. See comment K

Redacted see comment F

The criticisms are made by people with conflicts of interest is a reflection of a lack of insight. See comment E

How to move forward? It depends of what the AJGP is. If the AJGP is a platform for excellence in current knowledge, then these papers are a poor reflection of the current knowledge and extensive correction should be done at least for paper 1 (or consider withdrawing it). You could consider commissioning a paper to a non-Australian melanoma group. See comment C

If the AJGP is a field for discussion, then ask Thompson et al to transform their letter in a paper to be published in the journal.

Redacted see comment F
Reviewer C

Overall summary

I have had a brief look over the material. I have not read all the articles in full. The lead author, Dixon, is an osteopath which is a small concern. **The lead author is not an osteopath and has no skills in osteopathy. He has medical degree, specialist qualifications as well as a PhD.**

I have not heard of the Australasian College of Cutaneous Oncology. **See comment C.**

The problem you have is that it is already published. One solution would be to publish the letter from Prof Thompson and his co-authors and the response by Dixon and argue that vigorous debate exploring different perspectives is good for science. **It seems extraordinary that the AJGP would accept a review from someone who has not read the articles in full.**
Comments on reviews by authors of original two manuscripts

A) Experience / curriculum vitae of authors
The research and / or clinical experience of the authors of published manuscripts is not relevant and should not have been mentioned. Manuscripts are always to be evaluated on their content, not on the author(s). Indeed, medical students are entitled to write manuscripts. A recent publication in AIGP includes a medical student author. That a reviewer would choose to criticize the experience of the author ahead of the content of the manuscript is extremely concerning. This demonstrates a lack of the core knowledge of the process of manuscript review.

B) Concerns come from eminent experts
The background, training and expertise of those expressing concerns about a manuscript is not relevant. As in comment (A) above, the judgment must be made on the content of the manuscript. The concern must be judged on its merits as assessed in the manuscript, not on who raised the concern.

C) Impossible to resolve these issues
The only issue that is the subject of concern for a reviewer in this circumstance is to evaluate whether or not a manuscript is substantially flawed as to require retraction. Differences of opinion and variations in data interpretation are managed by letters to the editor, allowing the reader to read the areas of controversy and evaluate the material for themselves. This is invariably followed by a response from the authors. From there the journal invariably allows the matter to rest. Such a standard process was required in this case.

D) Differences of opinion
The letter of concern by Thompson et al. may have pertinent and well cited alternative arguments. Dr. Thompson may believe their points are valid. Alternative positions can be managed through a letter to the editor. The reviewer’s task is to identify clear flaws in a manuscript and determine whether they are of such gravity as to require retraction. A disagreement is not a flaw. The reviewer would need to identify and detail each and any flaw. There has been no attempt to identify and / or elaborate on any flaws in either manuscript. The reviewer merely identifies that there are differences of opinion.

E) Association with pharmaceutical companies / conflicts of interest
Many of the authors of the Cancer Council web site guidelines have conflicts of interests associated with pharmaceutical companies. This is not an aspersion by the authors. This is fact. These associations can be found on the Cancer Council web site here: https://wiki.cancer.org.au/australia/Guidelines:Melanoma/Conflict_of_interest_register
It is a requirement of any researcher with such conflicts to declare such conflicts. No author of the letter of concern from Thompson et al declared such a conflict of interest. That we should be criticized by pointing out this failure is without explanation.

F) The final (part 3) manuscript submitted by the ACCO team.
That any discussion of our part 3 manuscript submission has been mentioned in this review is inappropriate. The AIGP editor in chief commissioned us to write two manuscripts in November 2018. He commissioned us to write a third manuscript in July 2019. This was not prepared as a rebuttal to Prof. Thompson. The Editor in chief advised that the letter from Prof. Thompson was not going to be published by the journal and as such, no response from us is required. That further areas of education for GPs on melanoma education had been identified suggested a further manuscript would be useful to the readership. That was the position of the Editor in Chief and the ACCO team. At no stage were we asked to provide a rebuttal to the Thompson complaint. At no stage did we do so. We were only aware that our first two manuscripts were even being considered for retraction AFTER they were retracted. Any reviewer assessing whether or not manuscript 1 or 2 should be considered for retraction must base that decision purely on the contents of manuscripts 1 and 2. That such a reviewer would even be shown our submitted part 3 is of concern. Part 3 should have been sent to independent blinded reviewers. This clearly did not happen. Because no material of our part 3 manuscript should have been involved in the retraction consideration process, all aspects pertaining to manuscript 3 have been redacted from these reviews. Had the ACCO team merely wrote a rebuttal as suggested above, we would have exercised minimal effort, as much less is required for an document not intended for publication. However, manuscript 3 was never a rebuttal. As a full structured manuscript our ACCO team collectively put hundreds of hours into its careful preparation. It seems apparent now that part 3 was never considered in the required formal process.
G) No surgery for second primary.
The reviewer concludes that it cannot possibly have happened that a patient was advised they did not need wide local excision of a second primary because they were on adjuvant therapy. Indeed this happened disappointingly frequently. In Dr. Dixon’s Geelong practice, many patients were advised by a particular medical oncologist that WLE of a second primary was not needed when they were on melanoma drugs. Dr. Dixon found himself trying to persuade his melanoma patients that each primary melanoma needed management by WLE regardless of a past melanoma or drug therapy. Dr. Dixon was alarmed by this misperception of the role of melanoma drugs. As a consequence, he added this point in GP melanoma education discussions. We found that many GPS had experienced oncologists giving this incorrect advice to patients. As such, this clarification was a needed addition to manuscript 1.

H) Citing papers presented at congresses that are yet to be published
The ACCO team would never cite material that was not published in a peer reviewed journal. Manuscripts 1 and 2 were prepared in December 2018 and early January 2019. We acknowledge that since submission, further trials have provided more evidence of long-term outcomes of melanoma drug therapy. Our conclusions were accurate based on evidence at the time. Papers presented at congresses have not necessarily been through a peer review process. We are all too familiar with interesting papers being presented at meetings only to find they never subsequently appear in any peer reviewed journal. To cite on congress presentations is not acceptable.

I) SLNB must be undertaken at the same time as wide local excision
This is the considered belief of some clinicians, but not others. There are several studies showing that SLNB can be effectively undertaken subsequent to wide local excision. For example:
There is also the recently published study:
Ironically we had heard this study presented at a meeting prior to our manuscript preparation. It had not been published at that time and hence was not considered for citation in our manuscripts. We considered the area of whether or not SLNB and WLE must be at the same time as most uncertain, hence not worthy of inclusion.

J) Can fine needle aspirate and ultrasound detect nodal involvement?
Our review has identified substantial research manuscripts published since 2000 on the topic of ultrasound and/or fine needle biopsy in detecting early melanoma involvement (Appendix 1). Is the reviewer suggesting that all these researchers do not understand the basic biology of melanoma in nodes? Further, the data is very clear that such nodal metastases detection does have prognostic implications. This is not “another topic” The very reason one does an US and FNA is to gain prognostic information, as is the reason for performing SLNB.

K) Personal abuse and insults at the ACCO team of authors
These comments are offensive and inappropriate. They do not relate to identifying faults in the two manuscripts considered for retraction. Our team has never suggested we are comparable to other experts in the field or otherwise. We prepared our manuscripts based on the evidence in published studies, not based on any expert opinions.

CONCLUSION
- The reviews above regarding possible manuscript retraction following the Thompson letter provide no basis for manuscript retraction.
- The reviews do not identify a single error in either retracted manuscripts.
- The reviews all contain personal insults and attacks on our ACCO research team
- We have been subjected to belittling and abuse regarding our research credentials, our experience, our judgment and our insight. There was no need for this. There is no place for this.
- There is no justifiable circumstance for any journal have accepted these reviews let alone acted on them.
5) APPENDIX 5 – Pertinent conflicts of interest of several authors of the Thompson letter
Conflict of interest register: Clinical Practice Guidelines for the Diagnosis and Management of Melanoma – Extract of document. The following doctors were all signatories to the Thompson letter.

Professor John Thompson
Executive Director, Melanoma Institute Australia
Consultancy fees/ honorarium: Honoraria received from GlaxoSmithKline, Bristol Myers Squibb, Proventus and Merck Sharp Dohme
Support for travel or accommodation: Travel support received from GlaxoSmithKline, Bristol Myers Squibb and Proventus

Professor Georgina Long
Medical oncologist, Melanoma Institute Australia; Professor of Melanoma Medical Oncology and Translational Research (MIA, University of Sydney, Mater and Royal North Shore Hospitals), NSW
Consultancy fees/ honorarium: BMS, Novartis, Roche, Amgen, Pierre Fabre, MERCK and Array
Support for travel or accommodation: BMS, Novartis, Roche, Amgen, Pierre Fabre, MERCK and Array
Other (e.g. registration fees for conferences, institutional interests, etc – see policy): BMS, Novartis, Roche, Amgen, Pierre Fabre, MERCK and Array

Dr Matteo Carlino
Medical Oncologist Westmead and Blacktown Hospitals, Melanoma Institute Australia Clinical Senior lecturer University of Sydney
Consultancy fees/honorarium: Board member Bristol Myers Squibb, MSD, Novartis
Travel support and registration fees from: Bristol Myers Squibb & MSD

Professor Richard Kefford AM
Professor of Cancer Medicine, Macquarie University
Support for travel or accommodation Support for conference attendance: Bristol Myers Squibb, Merck
Registration fees for conferences: Bristol Myers Squibb, Merck

A/Prof Alexander Menzies
Medical Oncologist, CINSW Senior Research Fellow, Melanoma Institute Australia, Royal North Shore Hospital, The University of Sydney
Consultancy fees/honorarium: Bristol Myers Squibb, MSD, Novartis, Roche, Pierre Fabre
Support for travel or accommodation ASCO 2017: Bristol Myers Squibb
APPENDIX 6) CONFLICT OF INTEREST DECLARATION OF THE AUTHORS OF THE RETRACTED MANUSCRIPTS

AUTHORS QUALIFICATIONS, AFFILIATIONS AND DECLARATIONS OF POTENTIAL CONFLICTS OF INTEREST

Professor John B. Dixon PhD, MBBS, Dip obs RACOG, FRACGP, FRCP Edin
Professorial Fellow Baker Heart & Diabetes Institute, Melbourne
Adjunct Professor:

Iverson Health Innovation Research Institute, Swinburne University
Primary Care Research Unit, Monash University, Melbourne, Australia

JBD declares that he is a consultant to Novo Nordisk, I-Nova, Bariatric Advantage, and Reshape. He is on a speaker panel and chair the Optifast Advisory board for Nestle Health Science. He is a co-director of the annual Minimally Invasive Surgery Symposium in the US. He has received research support from the NHMRC, RACGP and BUPA in recent years. He is a member of the steering committee member of NHS England funded By-Band-Sleeve study, and part of the Teen Labs research consortium funded by the NIH. He is on the speaker panel for HealthEd GP education. He is co-editor in chief of the Current Obesity Reports. These conflicts are all in relation to his obesity related research. In the area of skin cancer research, he has no conflicts to declare, and has never received any income in relation to work with ACCO over many years.

Dr Stuart Anderson, MBBS(hons), FRACGP, FARGP, FACCO
General Practitioner, Maffra Medical Group
Chair, Australasian College of Cutaneous Oncology
Medical Educator, Eastern Victoria General Practice Training
Visiting Medical Officer, Central Gippsland Health
Teaching Associate, Monash University
No conflicts of interest to declare.

Professor Anthony J Dixon, PhD, MB BS, FACRRM, MAOCD, DipRACOG
Academic in cutaneous oncology
Honorary Professor: American Osteopathic College of Dermatology
Director of dermatology education: Australasian College of Cutaneous Oncology
No conflicts of interest to declare.

Dr Alexander Nirenberg MBBS, BSc, FRCPath, FRCPA, FIAC, Diploma in Dermatopathology
Dermatopathologist, Dorevitch Pathology
Pathologist and APP, Jolimont Laboratory
Holiday relief pathologist, Cutaneous Pathology
Board Member and Director of Pathology Education, Australasian College of Cutaneous Oncology
Pathology Vice President, Australasian Dermatopathology Society
Pathology Tutor, University of Melbourne
Australian Representative, International Committee for Dermatopathology
I occasionally provide opinions on pathology cases from pathologists in other pathology laboratories, some on a fee for service basis (I have no formal arrangements with any laboratory for this).
Past Panel Member, Avant Medical Experts Committee
Past Member, Medical Advisory Committee, Masada Hospital
Past Member, Medical Advisory Committee, John Fawkner Hospital
Past Assessor, Breast Screen Victoria Performance Indicator and Standards Project
I declare that I have no conflicts of interest. I do not have any affiliations with industry and I do not receive any financial or other benefits from any industry or organisation apart from either salary or fee for service from some of those listed above.

Associate Professor Howard Steinman, MD, FAAD.
Associate Professor of Surgery, Campbell University School of Osteopathic Medicine
Mohs surgeon, US Dermatology Partners, Texas.
Fellow, American College of Mohs Surgery
No conflicts of interest to declare