Optimising treatment for Australian melanoma patients can save taxpayers millions of dollars annually

TO THE EDITOR: Patients with BRAF-mutated metastatic melanoma benefit greatly from the novel BRAF inhibitor dabrafenib and the checkpoint inhibitor ipilimumab, recently listed under the Australian Pharmaceutical Benefits Scheme (PBS). Dabrafenib results in rapid responses; but the cancer later adapts, and patients relapse rapidly. Conversely, ipilimumab slowly reactivates anticancer immunity, meaningfully improving long-term survival (up to around 20% at 5 years).

The costs of these drugs are substantial. Dabrafenib costs A$6759 per month, and median duration of therapy is 9.4 months.1 The Australian price of ipilimumab is confidential, but potentially up to A$190 000 per patient, depending on weight. The 2014 year-to-September PBS cost of ipilimumab was $68 456 890 (data from https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml).

Current PBS approval mandates that dabrafenib may only be used as first-line therapy. Commencing treatment with dabrafenib then switching to ipilimumab when the disease progresses may inadvertently deliver worse outcomes than using the slower but longer acting immunotherapy followed by the potent but impermanent BRAF inhibitor.2,3 After a BRAF inhibitor fails, there is often insufficient time to deliver the full course of ipilimumab, let alone for the immune system to reactivate. While some patients’ symptoms necessitate a BRAF inhibitor upfront, most are well enough to take ipilimumab first, with dabrafenib in reserve.4

Formal randomised trials of these sequences are underway (NCT01940809, NCT01673854, NCT02224781) but our clinical experience and two international case series reinforce that administering ipilimumab then a BRAF inhibitor is very likely to be superior. (Patients treated with BRAF inhibitor then ipilimumab: objective response rate, 0; stable disease, 6%; progressive disease, 94%.)2 BRAF inhibitor then ipilimumab v ipilimumab then BRAF inhibitor: overall survival, 9.9 months v 14.5 months; $P = 0.04.$2

In the absence of a formal economic analysis, we assume most of the approximately 1500 Australian patients who will die with metastatic melanoma every year accept treatment,3 Forty-six per cent of these patients have BRAF-mutated melanoma;6 and of these, 85% are well enough to defer treatment with a BRAF inhibitor. Thus, about 385 patients receive a potentially inferior treatment sequence, and around $36 million per annum of otherwise effective treatment is administered inefficiently.

Other countries with publicly funded health care (eg, the United Kingdom) do not restrict treatment sequences in metastatic melanoma. We argue that, until randomised trials identify inferior or superior sequences, Australian melanoma patients and taxpayers would benefit from flexibility in prescribing these breakthrough treatments.

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Correction

Incorrect provenance statement: In “Chronic suppurrative lung disease and bronchiectasis in children and adults in Australia and New Zealand: Thoracic Society of Australia and New Zealand guidelines” in the 19 January 2015 issue of the Journal (Med J Aust 2015; 202: 21-23), the provenance statement incorrectly stated that the guidelines were not peer reviewed. The guidelines were externally peer reviewed.
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Termination of pregnancy: a long way to go in the Northern Territory

TO THE EDITOR: The Northern Territory’s reproductive health services are fraught with access problems due to remoteness and disadvantage. Staff shortages and high staff turnover in the health workforce are well known.1 With the recent resignation from the public health system of the main termination of pregnancy provider in the Top End of Australia, women’s access to basic reproductive health services could be severely diminished and complicated.

Each year, about 1000 women undergo a termination of pregnancy in the NT. The only
remaining services providing termination of pregnancy in the NT include one private hospital (at which a few doctors can provide surgical abortions) and one public hospital (Alice Springs Hospital, at which a couple of doctors can provide surgical abortions). Each week, about 20 women present to the public health system in Darwin for a surgical abortion in their first trimester. These women no longer have public access. The question is who will provide this procedure?

One possibility is that women may have to be flown interstate for this procedure. Some state laws prevent this — for example, South Australian law has residency limits on the provision of termination of pregnancy. Also, interstate travel poses a considerable burden for women and girls in terms of delays, logistics and increased stress, and is not cost-effective for the health system.

How acceptable this arrangement will be to women in the NT is yet to be tested. But we already know that women who feel compelled to end their pregnancies will do anything regardless of how demeaning, undignified or dangerous it is.2,3

Another solution would be to reform the Medical Services Act (NT) as in force at July 2014, which prohibits the practice of early medical abortion using misoprostol and mifepristone outside of a hospital setting, thus precluding ambulatory early medical abortion. Currently, the Act limits provision of abortion to obstetrics and gynaecology specialists and limits the type of procedure to surgical methods only. If the Act were reformed, it would be possible for general practitioners in various primary health care settings to provide information and prescriptions for early medical abortions.

There is overwhelming medical evidence showing that early medical abortions are efficacious, safe and well accepted.4,5 In terms of the health system, shifting the task to GPs and freeing up precious theatre resources would be far more cost-effective than flying patients or doctors interstate.

However, the political reality is that politicians are often reluctant to step into the perceived controversy of reproductive health rights for their constituents.

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Pharmaceutical sales strategies and sponsorship

To the Editor: It is with dismay that we read in MJA InSight Morton’s dismissal of the international “No Advertising Please” campaign, citing Australian Medical Association (AMA) policy.1 Drug company sales representatives and their sales techniques influence doctors. Morton dismisses the 2010 systematic review2 through selective quoting of the editorial position. In fact, the editors supported the conclusion of the systematic review that there is no evidence of improvement and some evidence of adverse consequences from marketing. There is an abundance of evidence in the behavioural science literature on the impact of marketing,3-5 and there is evidence that marketers may not make doctors aware of the risks of their products.6

The influence of doctors who are paid by pharmaceutical companies to present research at conferences and workshops is also cause for concern. If we, as a medical community, decline to see sales representatives, will we see an increase in the funding for doctors to present to other doctors on behalf of the pharmaceutical industry?

Many, including AMA leaders, suggest we should continue in the current fashion. We dispute this.

We have the following practical suggestions:

• front-line clinical doctors, including busy general practitioners, should use the up-to-date, evidence-based information provided by the National Prescribing Service;
• doctors should obtain further information from authoritative evidence-based clinical guidelines available online, such as “Therapeutic Guidelines”; for future research funding, we advocate structures that more clearly separate the financially vested company from the researchers;
• conflict of interest statements should be provided beside the authors’ names in conference abstract lists; and

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• workshops should provide written disclosure to participants of the presenting doctors’ current and previous funding sources.

We support the “No Advertising Please” campaign. We also support further consideration of the insidious influence of pharmaceutical companies at conferences and workshops through their sponsorship of doctors.

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TO THE EDITOR: Fasting diets have been used by humans for millennia for religious and medical purposes and are now gaining popularity for wellbeing and weight loss purposes. With increasing use of short- and long-term courses of medication to manage a multitude of conditions, a question that needs to be asked is will fasting diets impact on medication regimens?

The 5:2 diet, where calorie intake is unrestricted 5 days a week and limited to 500 calories for women and 600 calories for men 2 days a week, is becoming increasingly popular due to widespread publicity. In humans, there is some evidence that intermittent fasting (mainly alternate day fasting rather than the 5:2 regimen) could lead to weight reduction, decreased insulin resistance and prevention of type 2 diabetes.1,2 It is possible that patients who are taking medication and intermittently fasting each week could encounter adverse effects or therapeutic failure.

It is possible that patients who are taking medication and intermittently fasting each week could encounter adverse effects or therapeutic failure. Medications of concern generally fall into two categories: those for which absorption may be significantly altered by administration on an empty stomach, and those for which increased gastrointestinal3 or other4 adverse effects may result when taken on an empty stomach (Box).

For example, the bioavailability of telaprevir when taken while fasting is 27% of that when taken with a standard meal.5 As telaprevir needs to be taken three times a day for 12 weeks for treatment of chronic hepatitis C, treatment failure may result with intermittent fasting.

On a similar note, while the absorption of warfarin is not adversely affected by fasting, it is possible that an altered diet (particularly a diet that is high in vitamin K-containing foods) in patients taking warfarin may lead to volatility in international normalised ratio.6

Caution is warranted for patients with diabetes who wish to embark on these fasting diets, despite the appeal in terms of weight loss and reduced insulin sensitivity.7 Glibenclamide, glimepiride and insulin carry a high risk of hypoglycaemia if continued as normal when fasting.7

We urge all health professionals to consider the possible impact of fasting diets on medications and investigate further where required. Information regarding potential clinical significance of the diet may be evaluated via the full product information for individual medications and through community and hospital pharmacies.

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The effect of fasting diets on medication management


Medications that warrant further investigation in patients undertaking fasting regimens*

<table>
<thead>
<tr>
<th>Medications for which adverse effects may be increased if taken while fasting</th>
<th>Medications for which there may be clinically significant alterations in absorption if taken while fasting</th>
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<tbody>
<tr>
<td>Corticosteroids, mycophenolate, tacrolimus</td>
<td>Itraconazole capsules, posaconazole</td>
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<tr>
<td>Doxycycline, metronidazole, sodium fusidate, tinidazole, sulfamethoxazole—trimethoprim</td>
<td>Atazanavir, darunavir, tenofovir, etravirine, ritonavir, saquinavir, valganciclovir, telaprevir, boceprevir</td>
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<tr>
<td>Clomipramine, fluvoxamine, paroxetine, venlafaxine</td>
<td>Acitretin, isotretinoin, tretinoin</td>
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<tr>
<td>Amantadine, bromocriptine, levodopa</td>
<td>Albendazole (for systemic infections only), griseofulvin, ivermectin, mebendazole, praziquantel</td>
</tr>
<tr>
<td>Baclofen, betahistine, cyproheptadine, dapsone, lithium, sodium valproate, tiagabine</td>
<td>Mefloquine, artemether—lumefantrine, atovaquone</td>
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<tr>
<td>Imatinib</td>
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<td>Cinacalcet, spironolactone</td>
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*This list is not exhaustive. •
Reassessment of the new diagnostic thresholds for gestational diabetes mellitus: an opportunity for improvement

To the Editor: With reference to d’Emden’s recent article,1 we believe the value of an internationally agreed set of guidelines has not been considered. The World Health Organization endorsed the new diagnostic criteria for the diagnosis of gestational diabetes mellitus (GDM) as suggested by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), and adopted by the Australasian Diabetes in Pregnancy Society (ADIPS),2 the Royal Australian and New Zealand Society of Obstetrics and Gynaecology, the Australian College of Midwives, the Australian Diabetes Society, the Australian Diabetes Educators Association, Austria, Canada, China, Germany, Greece, Israel, Italy, Japan, Poland and some organisations in the United States. The benefit of an internationally agreed set of guidelines for the diagnosis of GDM cannot be understated. It would allow for a consistent approach to the definition, and provide a consistent baseline on which to answer many of the unanswered questions about GDM. As with all consensus agreements, it is likely to change over time to reflect evolving research.

The potential increase in the number of women diagnosed with GDM has been considered by the IADPSG.3 Given the current diabetes epidemic, the prevalence of GDM should reflect the prevalence of glucose intolerance in the mature adult population.

The new guidelines have been carefully considered by the international community and are consistent with a large observational study and Level 1 evidence from two well conducted clinical trials,4 with controversies raised by d’Emden debated for several years.3 ADIPS supports the common understanding that will be enhanced by international consensus.

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about the new diagnostic criteria for gestational diabetes mellitus (GDM). In his article, he states that “women may be charged higher life insurance premiums because of a prior diagnosis of GDM.” A similar un referenced concern was also expressed in 2013.

We specifically examined this aspect in an Australian context. Twelve life insurance companies, responsible for more than an estimated 90% of the Australian retail life insurance market, were surveyed with a request from a hypothetical applicant. This applicant was a 40-year-old woman, with no current health problems, who had an episode of GDM 10 years earlier and a subsequent normal result on an oral glucose tolerance test. Ten of the twelve companies (83%) responded, and were unanimous that no additional insurance premium would be required.

The new Australasian Diabetes in Pregnancy Society criteria are likely to result in an increased prevalence of GDM. Logically, this may lead to an increase in the cost of initial treatment, but this cost may effectively be recovered by better obstetric outcomes. Local data are required.

It is inevitable that any change will be accompanied by differences of opinion. Whenever possible, these opinions should not be alarmist.

Anna S Y Zheng MB BS, Tony O’Leary FCIL, FAMS, Fellow(ALUCA)

In reply: Callaway and McElduff are dismissive of the concerns I raised in my recent article, asserting incorrectly that they are old arguments. The potential reduction of the risk of macrosomia (birthweight > 90th centile; large for gestational age babies) when one or more blood glucose levels (BGLs) on an oral glucose tolerance test are normal was only suggested recently, in February 2014. In response, new data confirmed the statistical flaw in the new diagnostic criteria for gestational diabetes mellitus (GDM). These data showed that (i) nearly 50% of women having only one elevated BGL test result do not reach the diagnostic risk threshold, and (ii) women having two or more BGL results just below the new diagnostic levels may be at greater risk, yet will not be identified.

The many international organisations mentioned by Callaway and McElduff were early adopters of the new criteria, and the impact of this interaction was not considered. Australia has an opportunity to develop a better, statistically valid, diagnostic approach. The rate of GDM and its management can then be benchmarked against other countries that have adopted the new statistically flawed diagnostic criteria. The benefit of this approach cannot be understated. Zheng and colleagues question the statement that it is a concern that

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