Short report

Knowledge of non-invasive prenatal testing among pregnant women

To the Editor: Non-invasive prenatal testing (NIPT) for trisomy 21 and other chromosomal abnormalities using cell-free fetal DNA became available in Australia on a user-pays basis in 2012.[1,2] Since then, the price of this highly accurate screening test has fallen as multiple international providers entered the market, including, earlier this year, the first Australian provider.[1,3] The growth in the industry and anecdotal evidence both suggest that demand for the test is increasing rapidly.

We undertook a brief survey in a convenience sample of women attending a specialist obstetric ultrasound service located in Perth, Western Australia, for first trimester screening (FTS) between February and April 2015. Ethics approval was provided by the Curtin University Human Research Ethics Committee. The median age of the women was 32.7 years, and 29.1% were of advanced maternal age (over 35 years); 84.3% of the women were of European ancestry; 95.9% of the pregnancies were singletons. Sixty-two per cent of the respondents (139/224) had been aware of NIPT before attending for FTS. Women aware of NIPT were asked whether they had already given blood for NIPT; 38/139 (27.3%) responded that they had. We believe, however, that some women may have believed that the blood collected for FTS was to be used for NIPT, showing a lack of understanding of the FTS process and the distinction between blood collection for FTS and NIPT. Of the women who stated they had not already used NIPT (and excluding another three who did not answer the question), 7.1% (13/183) indicated that they would definitely have NIPT, with a further 74.8% (137/183) indicating that a decision to have NIPT would be based on their FTS results. Of the women who had used NIPT or indicated they would consider using it, 74.4% (154/207) reported they would be willing to pay at least $400 for the test.

The results of this brief convenience survey highlight the high level of NIPT awareness among pregnant women and illustrate the potential demand for this test, but also raise issues about the patients' understanding of screening processes and of the role of NIPT in the screening pathway.

There is currently neither a national approach to NIPT, nor are there recommendations about how NIPT should be integrated into the prenatal screening pathway in Australia, although work is underway.[4] Screening strategies that have been proposed include providing NIPT in combination with an ultrasound examination to all women, as an alternative to FTS; offering NIPT to women with pregnancies identified by FTS as high-risk (estimated risk of trisomy 21 of greater than 1 in 300); or, as a variation of this second strategy, offering NIPT contingent on an FTS result, but using more sensitive risk cut-offs.[5]

Steps should be taken to ensure that women are adequately informed about their prenatal screening choices, the potential pathway resulting from screening, and the benefits and limitations of these tests.

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> "demand for the test is increasing rapidly"
>
> Maxwell et al

> "TEN represents a minute fraction of significant adverse reactions to contrast medium"
>
> Ridley et al

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Toxic epidermal necrolysis — an investigation to dye for?

To the Editor: We thank Ly and colleagues for the case report entitled "Toxic epidermal necrolysis [TEN] — an investigation to dye for",[1] and make the following comments.

First, the authors state that the link between iopamidol exposure and subsequent TEN in their patient was confirmed by the Therapeutic Goods Administration (TGA). The TGA collates the Database of Adverse Event Notifications, a repository of adverse events associated with medication exposure. Inclusion in the database does not require proof of causality; in fact, the TGA states that reports reflect individual observations and that there "might be no relationship between the adverse event and the medicine".[2] Although the authors correctly identified this as the first submission regarding iopamidol and TEN, it is inaccurate to assert that it was confirmed by the TGA.

Second, Ly et al[1] described their case as a "late adverse reaction" to the contrast medium. The American College of Radiology defines delayed reactions as occurring between 1 hour and 1 week after exposure to contrast.[3] The literature cases of post-contrast reactions cited by Ly et al all occurred within 7 days of the injection, with the majority occurring within 24 hours. Although the mean interval between exposure and the onset of drug-related TEN has been reported to be as long as two weeks,[4] the algorithm of drug causality for epidermal necrolysis (ALDEN) stipulates that causation is doubtful if the suspected agent has been discontinued for longer than five times the elimination half-life of the medium.[5] Iodinated contrast media, including iopamidol, are predominantly excreted via the kidneys, with a half-life of 2 hours. Notably, European Society of Urogenital Radiology guidelines suggest that 50% of presumed late adverse reactions are subsequently found to be unrelated to contrast media.[6]

Ly et al concluded that iopamidol was "highly likely" to have caused the described reaction in their patient. In view of the 4-week interval between exposure and symptoms, however, other causes, including indapamide and the herbal supplement used by the patient, need to be considered.

In conclusion, TEN represents a minute fraction of significant adverse reactions to contrast medium, and in itself is not a reason to reconsider using contrast. We thank Ly et al for highlighting the life-threatening nature of this reaction and the challenges in determining the causative agent.

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Hereditary leiomyomatosis and renal cell carcinoma syndrome

To the Editor: A 52-year-old woman was referred in 2003 for cutaneous examination following excision and radiotherapy of a left tonsillar squamous cell carcinoma in 2000. Her personal history was remarkable for her developing asymptomatic cutaneous nodules since the age of 20 years and uterine fibroids requiring hysterectomy at 28 years; she underwent bilateral oophorectomy for symptomatic ovarian cysts at the age of 48. She had a family history of early-onset uterine fibroids.

Physical examination revealed multiple firm red papules and nodules on her forearms, abdomen and legs (Box 1, A, B), clinically consistent with benign smooth muscle tumours (leiomyomas).

> "this rare condition is caused by a mutation in the fumarate hydratase ... gene"
>
> Chinniah et al

A right arm lentigo maligna melanoma and multiple basal cell carcinomas were also detected.

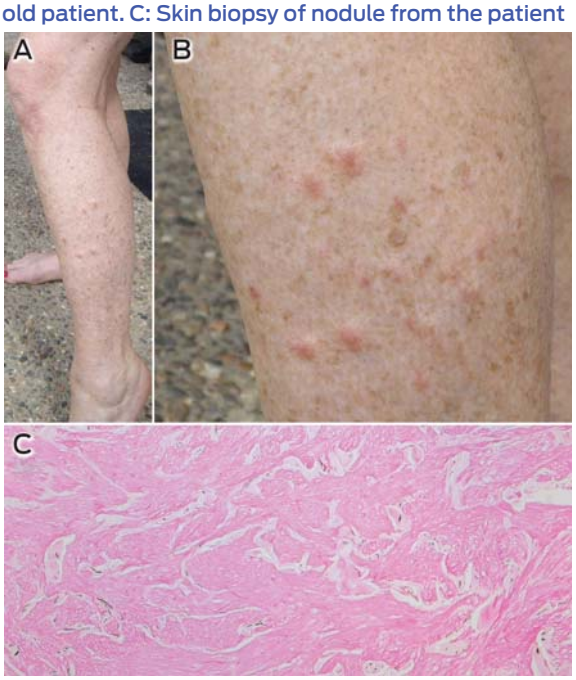
Skin biopsy of a long-standing nodule revealed that the dermis was filled with irregular fascicles of pleomorphic smooth muscle cells that infiltrated the collagen bundles (Box 1, C), consistent with leiomyoma.

Over the following decade, the woman developed multiple benign bowel polyps, a fibroadenoma in the right breast, a lobulated cyst in the left kidney, and a lentigo maligna melanoma on the left thigh.

Her presentation was suggestive of hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC). This rare condition is caused by a mutation in the fumarate hydratase (FH) gene on chromosome 1q. FH catalyses the conversion of fumarate to malate and acts as a tumour suppressor gene.[1,2] In our case, mutational analysis revealed a heterozygous FH:c.302A>C variant in exon 3 of the FH gene.

HLRCC is inherited in an autosomal dominant manner, with

1 A, B: Papules and nodules on the leg of the 52-year-old patient. C: Skin biopsy of nodule from the patient



2 Diagnostic criteria for hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)[4]

Definitive diagnosis
- Confirmed mutation in the fumarate hydratase gene.

Major criterion
- Multiple cutaneous leiomyomas with at least one histological confirmation.

Minor criteria
- A single leiomyoma with a positive family history of HLRCC.
- Multiple early-onset uterine fibroids.
- Early-onset renal tumours (papillary type II).

The genetic finding confirms the diagnosis. HLRCC is strongly suggested by the presence of the major criterion and is supported by the presence of the minor criteria. ◆

more than 75 different mutations and 100 pedigrees reported worldwide. The prevalence of the syndrome, however, remains unknown. It is characterised by the development of multiple cutaneous and uterine leiomyomas, and skin lesions are the earliest feature. Importantly, renal malignancies develop in up to 16% of individuals.[3] Consensus criteria for the diagnosis of HLRCC are listed in Box 2.

Although the dermatologist often makes the initial diagnosis, multidisciplinary care of the patient and at-risk family is essential, and should involve the gynaecologist, urologist and geneticist. While no official guidelines exist, baseline screening for uterine and renal tumours by ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) can reveal the extent of disease. Follow-up surveillance includes cutaneous and pelvic examinations every 1–2 years, together with abdominal and pelvic ultrasound, CT or MRI assessments, depending on the medical centre. Treatment of the benign leiomyomas is elective.

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Heatwave and risk of heat-related burn injury to children in Western Australia

To the Editor: Hot weather causes heat exhaustion, sunburn and contact burns. Each summer, children with these injuries attend Princess Margaret Hospital for Children in Western Australia. The Commonwealth Scientific and Industrial Research Organisation has recently proposed a definition for heatwave, requiring 3 days or more of high maximum and minimum temperatures that are unusual for a specific location.[1] This is based on an excessive heat index numerical prediction model[2] that is being tested by the Bureau of Meteorology for heatwave forecasting.[3] Are local weather observations associated with an increase in these types of hot weather-related injury in children?

> “For every unit rise in excess heat, we saw 11% more cases of sunburn, 26% more cases of contact burns and 9% more cases of heat exhaustion”
>
> Martin et al

Data on heat-related injury were collected about severity, type, date, time and place of injury, and age and sex of the victim. Local weather readings were obtained from the Bureau of Meteorology for minimum, maximum and average daily temperatures (ADT) in degrees Celsius and for solar exposure in megajoules per square metre (MJ/m^2). We calculated excess heat using the sum of the ADT for the day of injury and the previous 2 days divided by three. Data were analysed by Poisson regression with STATA, version 12 (StataCorp). All models were adjusted for the summer period in each year, but this was not significant. No other adjustments were made.

Fifty-four children aged between 3 weeks and 15 years presented to Princess Margaret Hospital for Children with sunburn, contact burn or heat exhaustion in the 3-year period 1 January 2011 to 31 December 2013. There was a non-significant increase in the number of days in which heat-related injuries presented over this time. All three types of hot weather injury were associated with solar exposure recordings and with excess heat calculations. For every unit rise in solar exposure, there were 18% more sunburn presentations, 14% more contact burn presentations, and 16% more heat exhaustion presentations. For every unit rise in excess heat, we saw 11% more cases of sunburn, 26% more cases of contact burns and 9% more cases of heat exhaustion. Each of these results were statistically significant (Box).

The statistically significant association between hot weather recordings and these injuries means that heatwave forecasts in Perth could also predict an increased risk of these injuries, and thus could be used to trigger media messages about burn

prevention to raise community awareness. As heatwave forecasting is location-specific, our findings might not be transferrable to other locations.

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Eight challenges faced by general practitioners caring for patients after an acute coronary syndrome

To the Editor: We would like to comment on some important inaccuracies in Vickery and Thompson's article on general practitioner management of patients after an acute coronary syndrome.[1]

The authors state that unassisted cessation of smoking (quitting without professional support or pharmacotherapy) is the most effective method. In fact, it is the least successful method and produces quit rates of only 3%–5% at 6–12 months.[2] In comparison, the quit rate from combined counselling and pharmacotherapy ranges from 22% to 32%, depending on the intensity of counselling provided.[3]

Although many smokers ultimately quit without help, it is usually after numerous failed attempts. Each year that smokers delay quitting after the age of 35 results in a 3-month reduction in life expectancy.[4] It is therefore vital that smokers stop at the earliest possible opportunity and that every quit attempt has the best possible chance of success.

We advise doctors to follow the Australian[5] and United States.[3] smoking cessation guidelines, which recommend the use of pharmacotherapy and counselling for all nicotine-dependent smokers.

The authors have also misinterpreted the Cochrane review data for the efficacy of nicotine replacement therapy (NRT). They state that 50%–70% of people achieve abstinence with NRT. However, the absolute long-term quit rate is only 6%–12% more than for placebo.[6] The confusion may have arisen because NRT increases the rate of quitting by about 50%–70% compared with placebo.

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Association between type of heat-related injury in 54 children aged 3 weeks to 15 years and weather recordings

	Solar exposure		Excessive heat factor	
Injury	Incidence rate ratio (95% CI)	*P*	Incidence rate ratio (95% CI)	*P*
Sunburn	1.18 (1.07–1.30)	0.001	1.11 (1.01–1.21)	0.032
Contact burn	1.14 (1.00–1.29)	0.049	1.26 (1.09–1.46)	0.002
Heat exposure	1.16 (1.07–1.25)	0.000	1.09 (1.01–1.18)	0.029

> Each year that smokers delay quitting after the age of 35 results in a 3-month reduction in life expectancy
>
> Mendelsohn et al

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In reply: We thank Mendelsohn and Camp for their comments on our article. Their opinion on the best way to quit smoking may be relevant to some smokers, but it is not shared by all ex-smokers, nor by all other quit-smoking authorities.

In contemporary practice, 54% to 69% of Australian ex-smokers had quit unassisted.[1] Reservations about the adequacy of unassisted quitting are at odds with a 2013

Gallup poll in the United States, which showed that only 8% of ex-smokers attributed their success to pharmacotherapy, whereas 48% credited quitting "cold turkey".[2] Other internationally recognised Australian quit-smoking authorities have expressed the opinion that the impact of unassisted cessation on reducing smoking prevalence is underappreciated, and unassisted quitting should be considered before pharmacotherapy and other methods.[3]

The effect of social media campaigns on smoking cessation, an area in which Australia has considerable international leadership, may also be a major contributor.[4] We note that Mendelsohn and Camp promote pharmacotherapy not only in their letter, but also on Mendelsohn's "Smokers' Clinic" website,[5] without acknowledging that many patients successfully quit on their own. This is particularly so when patients have had a health shock such as an acute coronary episode, which was the context of our article. It has been shown that 57% of people who were smokers before an acute coronary syndrome were not smoking 8 months after their coronary event.[6]

We appreciate the correction to our statement on the efficacy of nicotine replacement therapy (NRT). Mendelsohn and Camp are quite right. The correct interpretation of the 2012 Cochrane review[7] is that NRT increases the rate of quitting by 50%–70%, and we acknowledge that long-term cessation success rates remain low.

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"only 8% of ex-smokers attributed their success to pharmacotherapy, whereas 48% credited quitting 'cold turkey'"

Thompson et al