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Nicotine metabolite ratio test as a predictor of smoking cessation

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PRIORITISING SUMMARY

REGISTER ID: **000230**

NAME OF TECHNOLOGY: **NICOTINE METABOLITE RATIO TEST MEASURING RATIO OF 3'HYDROXYCOTININE TO COTININE.**

PURPOSE AND TARGET GROUP: **SMOKING CESSATION PROGRAMS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☒	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada	✓		

IMPACT SUMMARY:

The nicotine metabolite ratio test of 3'hydroxycotinine to cotinine (3'HC/COT) may customise and improve treatment efficacy of nicotine patch therapy for smoking cessation. The test is not currently commercially available but could potentially be provided through public sector laboratories and/or hospitals.

BACKGROUND

Tobacco creates the highest burden of disease of any single preventable risk factor in Australia (Mathers 1999). Public awareness of smoking's harmful effects has been instrumental in lowering smoking rates. Addiction to nicotine is a challenge for a health promotion campaign approach to quitting smoking.

In smokers who are motivated to quit, nicotine patches increase the probability of success by 1.5 to 2 times (Silagy et al 2004). However recent evidence shows that the effectiveness of a tapered dose of nicotine is affected by individual rates of nicotine metabolisation, which has a partially genetic basis (Lerman et al 2006).

P450 2A6 is a liver enzyme that metabolises 70 to 80 per cent of nicotine into cotinine, and is encoded by the gene *CYP 2A6* (Benowitz et al 1994). This enzyme is also largely responsible for the metabolism of cotinine to 3'hydroxycotinine (Hukannen et al 2005).

A rapid nicotine metabolism reduces circulating levels of nicotine, and therefore higher amounts of nicotine must be consumed to satisfy cravings (Lerman et al 2006). In addition to increased difficulty abstaining, rapid metabolisers are at greater risk of adverse health effects associated with smoking, as they are likely to smoke an increased number of cigarettes to satisfy nicotine cravings (Minematsu et al 2003; Tyndale and Sellers 2002; Tyndale and Sellers 2001). Offering higher dosage nicotine patches to those identified with fast nicotine metabolism may increase the likelihood of smoking abstinence (Lerman et al 2006). The 3'HC/COT ratio as a predictor of nicotine metabolism therefore has the potential to increase the effectiveness of nicotine replacement therapy, as well as the individual confidence and willingness to use such therapy. The 3'HC/COT test may be conducted using high performance liquid chromatography (HPLC), gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/mass spectrometry (LC/MS) techniques (Dempsey et al 2004; Lerman et al 2006).

CLINICAL NEED AND BURDEN OF DISEASE

Even though daily smoking rates have decreased by 40 per cent between 1985 and 2004 (AIHW, 2005b), the burden of disease attributable to smoking remains high given the latency between exposure and adverse health effects. Smoking is responsible for 9.7 per cent of all death and disability in Australia (Mathers 1999).

Smoking has associations with increased morbidity and mortality from cancer, as well as respiratory and cardiovascular diseases. The proportion of deaths from cancer, ischaemic heart disease, and chronic obstructive pulmonary disease attributable to smoking are 40, 21, and 20 per cent respectively (Miller & Draper 2001). Of hospital separations relating to these conditions, 19, 26 and 20 per cent are attributable to smoking respectively (Miller & Draper 2001).

At best estimate, 22.5 per cent of low birth weight events may be attributed to smoking in pregnancy (Ridolfo 2001). Low birth weights are associated with a higher cost of antenatal care and adverse health effects for the children in later life.

Smoking carries a high economic burden in Australia. In addition to the enormous financial impacts on the health system, smoking has been associated with a decrease in productivity in the workplace (Ministerial Council on Drugs Strategy 2004). The personal economic cost of cigarettes also disproportionately affects people from lower socioeconomic backgrounds who are heavier consumers of cigarettes (AIHW 2005a).

The Australian Institute of Health and Welfare (AIHW 2005a) reported the prevalence of smoking in Australia in 2004 to be 17.4 per cent of the population over 14 years. This report estimated 25.9 per cent of Australian smokers had unsuccessfully tried to give up smoking in the past 12 months (AIHW 2005a). The population over 14 years in 2004 was 16,113,383 (Australian Bureau of Statistics 2006). Applying these statistics to population level data, 726,165 Australian smokers over 14 years had tried to give up smoking at least once in 2004. This would be the maximum number of people who could have used this test as an aid to stop smoking.

DIFFUSION

Currently tests to measure nicotine metabolism are not commercially available in Australia. It is most likely that the tests would be carried out in a laboratory setting such as in hospitals and public sector pathology laboratories such as South Australia's Institute of Medical and Veterinary Science (IMVS).

The nicotine metabolite ratio test is currently only in use as a research tool. It is likely to be more acceptable to smoking individuals in comparison with other methods used for the same purpose (Dempsey et al 2004), as it is minimally invasive and the methods of collection are commonly used for routine pathology tests. Specimens may be collected via plasma, saliva and urine (Lerman et al 2006) (see safety and effectiveness section).

COMPARATORS

Currently cotinine testing may be conducted in hospitals and public sector pathology laboratories. Cotinine testing does not measure nicotine metabolism, but it is the current method of determining the level of cigarette smoking (heavy, light etc). Central Sydney Laboratory Service list it for use as an aid for patient counselling in smoking cessation programs (Central Sydney Laboratory Service 2002). Cotinine testing is not funded under the Medicare Benefits Schedule. There is a 15-20% intra-individual variability dependent on the time since last cigarette (Central Sydney Laboratory Service 2002). Dempsey et al (2004) state that the plasma cotinine test has provided mixed results in trials as a predictor of smoking cessation.

EFFECTIVENESS AND SAFETY ISSUES

Dempsey et al (2004) showed that the ratio of nicotine metabolites 3'HC/COT in either saliva or plasma, is a predictor of nicotine metabolisation in current smokers, as shown by a high correlation with the oral clearance of nicotine and cotinine (Dempsey et al 2004). The average 3'HC/COT ratio is relatively stable over time within a smoking group. Due to this stability, the 3'HC/COT ratio can be detected without complicated pre-test procedures.

Lerman et al (2006) conducted a retrospective analysis of an unblinded randomised controlled trial (Lerman et al., 2004) assessing the effectiveness of two methods of nicotine replacement therapy (transdermal patch and nasal spray). The aim was to determine whether a baseline 3'HC/COT metabolite ratio test predicted smoking cessation: (1) independent of treatment method, and (2) by treatment method (Level III-3 prognostic evidence). The trial by Lerman et al (2004) compared the efficacy of the nicotine patch and nicotine nasal spray treatments for smoking cessation. Subjects were randomly allocated to either the nicotine patch or the nasal spray treatment for a period of eight weeks. The frequency of nasal spray use was at the liberty of the individual with between 8 to 40 sprays every day (no more than 5 sprays/hour), although the dose per spray was tapered. The initial dose instructed to be sprayed was 1mg. The dose was tapered by one third at four weeks after treatment and by another third at six weeks of treatment. The transdermal nicotine followed a tapered dose; 21mg patches were used in the first four weeks, which then was changed to a 14 mg dose for the following 2 weeks and then 7mg dose for the final two weeks of treatment. Seven behavioural therapy sessions were given to all subjects.

Subjects were measured at baseline for a number of factors thought to affect the efficacy of treatment. Lerman et al (2006) investigated the impact of these variables, particularly the primary prognostic variable of the 3'HC/COT ratio. Results showed that as the 3'HC/COT ratio increased, there was a reduced likelihood that there would be a prolonged abstinence from smoking (biochemically verified) in the nicotine patch group at end of treatment and at 6 months follow up. The results of the 3'HC/COT ratio were analysed in quartiles. For every quartile 3'HC/COT ratio increased, the quit rate decreased by approximately 28 percent [OR=0.72, 95%CI 0.57, 0.9]. There was no such observed effect in the nicotine spray group at end of treatment [OR = 1.05, 95% CI 0.83, 1.33]. This is likely to be because the nicotine spray group was self titrated, and therefore dosage could be compensated by perceived need. The nicotine spray was, however, less effective that the nicotine patch overall at end of treatment (Lerman et al 2006). The overall success at quitting in the nicotine patch group was higher at end of treatment (8 weeks duration) than at 6-months follow up. At 6-months follow up there was, however, a more noticeable decline in the success with every increasing quartile of 3'HC/COT ratio. Results were controlled for other baseline covariates, namely nicotine dependence, body mass index, race, and sex.

The study population was 65 per cent European, 28 per cent African American and 7 per cent other races. Differences between this group and the Australian population may also affect the external validity of the results, although it is likely that there is considerable overlap. Chinese, Koreans and Japanese have reduced activity polymorphisms of the *CYP 2A6* gene (Hukkanen et al 2005). Further trials are required to make inferences about whether this test is as strongly predictive for these groups. Other enzymes may become more important in their nicotine metabolism. This is not likely to be important in the sense of prescribing high dose patches to these people, but could be important in prescribing safe or tolerable doses in these groups.

Lerman et al (2006) suggest that the 3'HC/COT ratio could be used to increase the effectiveness of nicotine replacement therapy by customising an appropriate dose of nicotine in patches. Lerman et al (2006) recommend that subjects with a 3'HC/COT ratio 0.47 or above are more likely to benefit from higher dose nicotine patches than 21mg/24 hours, than those with a ratio below 0.47. Given the wide variability of nicotine metabolic rates, the potential may exist to customise nicotine replacement therapy over a wider range of doses that are currently available in Australia.

Lerman et al (2006) state that the nicotine metabolite test is testable in saliva, plasma, and urine. However testing in urine has more methodological issues than testing in saliva or plasma, as only 12 per cent of the cotinine present is excreted in urine, although 63 per cent of 3'hydroxycotinine is excreted (Hukkanen et al 2005). Extreme acidification of the urine can increase the percentage of cotinine excreted (Hukannen et al 2005). Using this fact to advantage, Dempsey et al (2005) designed a test whereby the amount of cotinine in the urine was increased by prior administration of ammonium chloride, although this increases the time and complexity of the test, and evidence was not provided upon its correlation with oral nicotine clearance.

The most likely testing procedures are likely to be a blood test or a saliva sample, therefore the safety issues associated with the testing procedure will be minimal.

If the test is used to titrate therapy over doses higher than 21mg/24hours as suggested by Lerman et al (2006), then issues of safety are not likely to be a problem. High nicotine

metabolism is associated with heavy smoking. The highest dose patches available in Australia are 21mg /24 hour in strength (Australian Medicines Handbook 2006). The safety of 44 mg/24 hour patches has been tested in a group of heavy smokers, who smoked greater than 20 cigarettes per day before the start of the trial (Fredrickson et al 1995). The study reported that no significant adverse effects were attributed to the 44 mg/24 hr dose. Smoking whilst using nicotine replacement therapy puts individuals at risk of nicotine overdose (Zwar 2004), though some participants smoked during the trial without adverse effect. However the group who reported sleep disturbances had a significantly higher mean cotinine level above baseline than those who did not report sleep disturbances. Increased baseline cotinine levels could be an indication of those who continued smoking during the trial, or it could indicate variable nicotine metabolism within this group. Although a 44 mg patch may cause overdose in light smokers, this study shows that in some people this dose may be appropriate, and shows the potential benefit of the 3'HC/COT test for identifying individuals with high nicotine metabolism for whom this dose may be safe and tolerable.

COST IMPACT

The technology being used is a high pressure liquid chromatography test (HPLC), or a gas chromatography-mass spectrometry test (GC-MS). HPLC in particular is a widespread technology in laboratories, and is relatively inexpensive. Procedures currently subsidised that use this technology include haemoglobin chromatography for investigation of haemoglobinopathy or thalassemia (Medicare Benefits Schedule item numbers 65078 and 65081). The fees for these tests are $98.25 and $91.75 respectively, although both tests may include other diagnostic techniques.

Other potential costs associated with tests may be the training of doctors and genetic counsellors on how to advise patients about their test results.

The benefits of using this test to titrate therapy may offset long term costs associated with smoking related diseases. Hospitalisations and expensive health technologies such as stents for coronary heart disease are among some of the many economic costs of smoking. A conservative estimate of the tangible costs of smoking in Australia for 1998-1999 is $7.59 billion, and intangible costs bring this figure substantially higher (Ministerial Council on Drugs Strategy 2004).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Education regarding the limitations and implications of the test should be given to counsellors, doctors, and patients would be required as the evidence base is very limited. This would be particularly important if its use was to titrate nicotine replacement therapy to improve smoking cessation.

The National Tobacco Strategy 2004-2009 outlines reduced access to health services such as doctors and pharmacies as a barrier to smoking cessation in rural and remote regions (Ministerial Council on Drugs Strategy 2004). Smokers in regional and remote regions also consume more cigarettes per week than city dwellers, and are more likely to be smokers (AIHW 2005a). Targeted health promotion and service provision may therefore be needed in these areas.

OTHER ISSUES

Lerman et al (2006) also suggest that those with fast nicotine metabolism may consider another form of therapy in addition to nicotine replacement therapy.

There is intra-individual variability of nicotine metabolism and this may be determined by such things as menthol in cigarettes, and certain dietary factors such as grapefruit juice and wheat grass juice (Hukkanen et al 2005). Such information may bias the results of individual studies, and doctors and patients should be made aware of the known factors so as to avoid them prior to the test.

CONCLUSION:

One good quality level III-3 prognostic study was available to test the predictive ability of the nicotine metabolite ratio test for smoking cessation. There is no evidence available to test the effectiveness of this prognostic marker at guiding the titration of nicotine therapy for better outcomes.

HEALTHPACT ACTION:

Although the nicotine metabolite ratio test appears to be sufficiently predictive of smoking cessation, the practical benefits of the test are uncertain. It is likely that smokers who have difficulties quitting would benefit from higher dosage nicotine patches regardless of their nicotine metabolism. It is therefore recommended that this technology be archived.

SOURCES OF FURTHER INFORMATION:

No other issues were identified in the sources examined.

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LIST OF STUDIES INCLUDED:

Total number of studies	
Level III-3 Prognostic evidence	1

SEARCH CRITERIA TO BE USED:

Cotinine/analogs & derivatives/blood
Liver/enzymology
Nicotine/administration & dosage/blood/*pharmacokinetics
*Smoking Cessation