NicoTest™

The New Way to Quit

Notes for Medical Professionals

The Nicotest™ "is a model of how we should exploit basic research in the prevention of cancer"

Professor J Gordon McVie, MD, FRCP, FRCPS ,FRCSE, FMedSci, DSc(Hon)

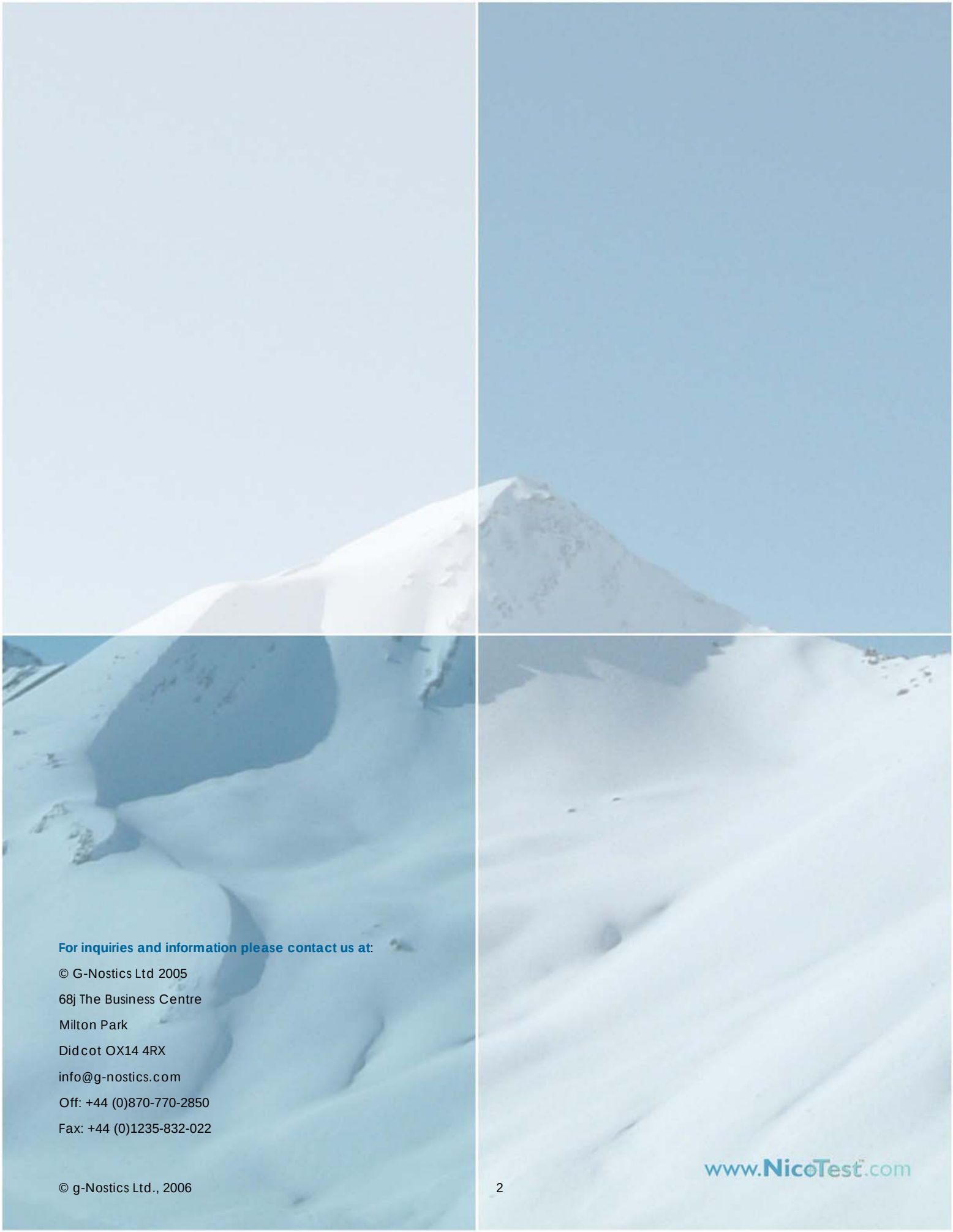
Director of the European Institute of Oncology, Milan

The Nicotest™ "approach to treating addiction to smoking is long overdue, and it is particularly pleasing that the power of these genetic technologies has become available to the public"

Michael Thick MA MB BChir (Cantab) FRCS (Lon) FRCS (Ed)

National Medical Director, National Programme for Information Technology at the Department of Health

www.NicoTest™.com



For inquiries and information please contact us at:

© G-Nostics Ltd 2005

68j The Business Centre

Milton Park

Didcot OX14 4RX

info@g-nostics.com

Off: +44 (0)870-770-2850

Fax: +44 (0)1235-832-022

www.NicoTest.com

NicoTest™

INDEX

What is the NicoTest Programme? 4

Overview of NicoTest™ 4

Increase quit rates by 4

Nicotest™ PIP Code, Regulatory Status and Kit Contents 4

How is the NicoTest™ different from other products on the market? 4

Two main components of the NicoTest™ programme: 4

1. Initial data entry and treatment recommendations 4

2. Online support programme (The Flight to Freedom) 4

How does it work? 5

Pharmacogenetics 5

NicoTest™ Computerised Cognitive Behavioural Therapy 7

Computerise decision support enables tailored dosing 8

Computerised cognitive behavioural therapy helps smokers quit 8

Personalised treatment can improve success rates 8

Independent academic and scientific comments on the Nicotest™ 8

Independently validated claims 9

1. Increase quit rates by using a structured smoking cessation programme 9

2. Increase quit rates by taking the right medication at the right dose 9

3. Increase quit rates by using professional support during the quit 9

4. Increase quit rates by combining medication and online support 9

5. Increase quit rates with Personalised Treatment 9

References 9

© g-Nostics Ltd., 2006

NicoTest™

WHAT IS THE NICOTEST PROGRAMME?

The NicoTest™ is an innovative smoking cessation programme combining Internet-based data collection, online cognitive behavioural therapy and a DNA-based diagnostic test to determine rate of nicotine metabolism and guide choice of treatment.

Using a simple computerised decision support system the Nicotest™ evaluates treatment options for each individual smoker and suggests a personalised treatment plan. Smokers trying to quit have 24-hour online support moderated by smoking cessation specialists and motivational text messages delivered to their mobile phone.

Overview of NicoTest™

Medical professionals strive to provide the best possible treatment for patients. The NicoTest™ is a systematic process to determine the most appropriate treatment plan for smoking cessation for each individual smoker.

The patient enters detailed data about his or her smoking habits into the secure Nicotest server. These data are then used to construct the personalised behavioural therapy programme for smoking cessation and also feed into the computerised decision support system which gives advice on treatment selection and dosage. The simple finger prick test, which is necessary for the DNA analysis, can be self-administered at home by the patient or in a supervised clinical environment. Information from this test is complementary to that given in the online questionnaires and, when processed by the computer system, enables the healthcare professional to make a personalised treatment recommendation. We believe that this new process will give your patient the best possible chance of quitting smoking.

Increase quit rates by

- using a structured smoking cessation programme
- taking the right medication at the right dose
- combining medication with online support
- using professional support during the quit attempt
- receiving motivational text messages and emails

Nicotest™ PIP Code, Regulatory Status and Kit Contents

- **PIP Code:** #3137593
- **Kit Contents**
  - Single use lancet
  - Safe Spot™ blood collection card
  - Antiseptic wipe
  - Plaster
  - Patient instruction leaflet
  - Pre-paid return envelope
  - NicAlert™ saliva cotinine self test strip
  - **Regulatory Status**

  - Components all CE marked
  - MHRA guidelines issued November 2004

How is the NicoTest™ different from other products on the market?

The NicoTest™ is a coordinated personalised treatment programme which blends our online support system with a diagnostic test to make sure that patient gets the right treatment and has the best chance of quitting. The Internet based behavioural programme *Flight to Freedom* (a metaphor we use to describe the quit process), helps smokers prepare to quit and then adapt to their new smoke-free lifestyle.

The NicoTest™ determines how the smoker's body might respond to different forms of medication (such as nicotine replacement therapy (NRT) or bupropion (Zyban). The DNA test estimates the individual metabolic rate for nicotine by determining common genetic variations in the enzyme that metabolises nicotine (CYP2A6). Each person has a different metabolic profile for nicotine that governs how quickly it is inactivated. An understanding of this unique profile will help you to give your patient the best advice about treatment selection and dosage. So for example you will know whether a patient metabolises nicotine slowly (Oscarson, 1999, Haberl, 2005, Yamano, 1990) and thus would require a relatively low replacement dose. The test also identifies people likely to respond well to nicotine replacement therapy (Johnstone, 2004) or be at higher risk of side effects using bupropion (Zyban) (Lerman 2003, Swan, 2005). This information is synthesised by a computerised decision support system to give your patient a personalised smoking cessation plan. There is evidence that such personalised plans may be effective ways of helping people to stop smoking (Lancaster and Stead 2002), and that computerised advice on drug dosage can increase the effectiveness of therapy (Walton 1999) and reduce side effects (Walton 2001).

The Online Support Program is an established computerised cognitive behavioural therapy programme that offers 24 hour support, seven days a week throughout the quit attempt.

Two main components of the NicoTest™ programme:

1. Initial data entry and treatment recommendations

- An online lifestyle and smoking history questionnaire (Milestones 1, 2 and 3 of the Internet based NicoTest programme) determines the smoker's level of nicotine dependence and identifies appropriate lifestyle changes that may be needed. This phase includes the Fagerström Test of Nicotine Dependence (FTND)
- A diagnostic tool that identifies a smoker's likely response to both nicotine and non-nicotine medications
- A Personalised Treatment Report that recommends the most appropriate treatment for each patient

2. Online support programme (The Flight to Freedom)

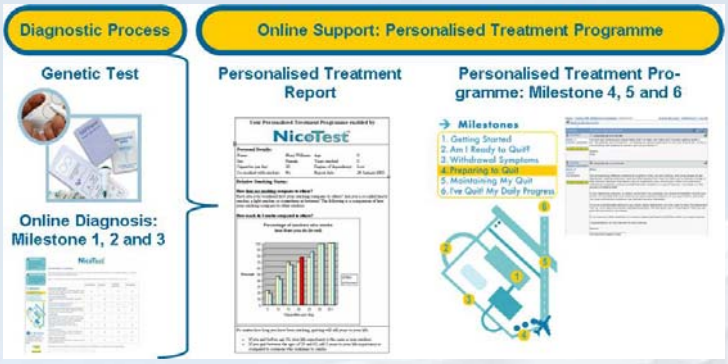
- An 11-week course of motivational emails commence after registration
- A professionally moderated, interactive, online support programme that encourages behavioural change and includes:

www.NicoTest.com

© g-Nostics Ltd., 2006

NicoTest™

- A QuitMeter that monitors the smokers nicotine dependence, financial savings and life years gained as they progress
- Coping plans to minimise weight gain, improve fitness and reduce stress
- A chat room to meet 'Buddies', using Internet Messenger to communicate with peers and interactive exercises to help the smoker prepare and adapt to their new smoke-free lifestyle
- Interactive activities to reinforce and maintain the quit process
- Follow-up survey to self-report progress and confirm effectiveness of treatment recommendations



NICALERT

The NicAlert™ compliments g-Nostics DNA-based NicoTest™ by validating the cessation progress of ex-smokers and identifies non-smokers at risk. The easy to understand visual read-out indicates the level of tobacco use or exposure within minutes and requires no instruments to use. NicAlert™ has received clearance from the U.S. FDA for determining smoking status for medical purposes and awaits a CE Mark.

Researchers at the Centers for Disease Control and Prevention (CDC) authored a study in the peer-review literature using NicAlert™ (*Journal of Analytical Toxicology* November/December, 2005; 29: 814-818). In the CDC study, NicAlert™ measurements correlated well with the far more complex laboratory testing (liquid chromatography-mass spectrometry) used in the CDC laboratory.

Other independent peer-reviewed studies have also found the technology employed in NicAlert™ to be accurate, rapid and cost-effective. One study, (*Cancer Epidemiology, Biomarkers & Prevention* 2002; 11: 1123-1125) found that the results obtained using Nymox's tobacco product exposure test had an "excellent agreement" with state-of-the-art sophisticated laboratory measurements but at a substantially lower cost (over 90% less). Another study, (*Nicotine & Tobacco Research* 2002; 4: 305-9) found Nymox's product to be "an inexpensive and rapid method to routinely biochemically confirm smoking status at a clinical visit".

- NicAlert™ is an extremely accurate point of care test for the level of exposure to tobacco products
- Detects nicotine from all tobacco products, second hand smoke and nicotine replacement products
- It tests for cotinine (a nicotine metabolite) in urine
- It uses a unique patented immunochromatographic technology
- It is a fast, inexpensive and easy to use disposable strip
- Requires no mixing or measuring of reagents, or calibration of equipment
- Does not require a machine or trained person to read
- Does not require first morning urine
- Does not detect drug use or cross react with other compounds

USE NICALERT™ TO:

- Identify which patients are smoking
- Detect second hand smoke exposure
- Measure level of nicotine dependency in smokers
- Assist patients in quitting
- Identify relapsed smokers

NICALERT™ FOR SMOKING CESSATION

- Readily demonstrates a biological effect to the smoker
- Shows their effect on others via second hand smoke
- Provides immediate feedback to doctor and patient on cessation activity
- Provides a positive objective measure for smokers trying to quit
- Provides a fresh tool to initiate counselling with the "not ready to quit" patient

HOW DOES IT WORK?

The NicoTest™ programme starts with a series of questions to establish the detailed smoking topography and collect basic demographic information. These questions ascertain the smoking history and help to determine why the smoker smokes. This information is essential for the online cognitive behavioural programme and is coupled with the results from the DNA analysis to find out the best way for the smoker to stop smoking. The Nicotest™ provides a 'personalised' programme for smoking cessation that is specific to the individual. The cognitive behavioural therapy program uses a metaphor which we call the *Flight to Freedom* and breaks the quit process into six Milestones. Registrants need to complete the DNA test and Milestones 1, 2 and 3 before we can issue the Personalised Treatment Report.

PHARMACOGENETICS

It has been estimated that about 50% of the initiation of smoking behaviour is genetically determined, whereas the genetic contribution to maintenance of smoking and the amount of tobacco smoked is approximately 70% (reviewed by Tyndale & Sellers, 2002).

These same genes may affect response to therapy for tobacco dependence together with a range of other genes influencing response to specific drugs. Individual genetic differences are being increasingly recognised as explaining why some people respond well to treatment with particular drugs and some do not. A general

© g-Nostics Ltd., 2006

review on the potential for pharmacogenetics in the provision of tailored programmes for smoking cessation is provided by Walton et al. (Walton et al. 2001).

Genetic Variation in the gene encoding CYP2A6 – the enzyme that metabolises nicotine

The cytochrome P450 2A6 (CYP2A6) enzyme is responsible for the majority of the metabolic inactivation of nicotine by conversion to cotinine.

There is considerable inter-individual variation in CYP2A6 activity. Individuals carrying inactive CYP2A6 alleles have a decreased rate of nicotine metabolism. These individuals may be less likely to become smokers or, if they do smoke, smoke fewer cigarettes per day. Conversely, a duplication variant in the gene encoding CYP2A6 increases nicotine inactivation and increases the amount of tobacco smoked (reviewed by Tyndale & Sellers, 2002).

CYP2A6 is expressed mainly in the liver and in trace amounts in extrahepatic tissues. It represents between 1% and 10% of the total liver P450 protein. The enzyme metabolizes several xenobiotic substances, including nicotine and its metabolite cotinine. It is possible that low CYP2A6 activity might protect against cancer because of reduced activation of carcinogens although the size of the effect, if any, is not certain (Haberl, M., et Al, 2005).

To date, five alleles (*2, *4A, *4B, *4D, *5), of which the deletion allele CYP2A6*4A is the most prevalent, are known to abolish the enzyme's activity. A further six alleles (*6, *7, *10, *11, *12, *17) lead to reduced enzyme activity. Recently, three genetic polymorphisms in the promoter of the CYP2A6 gene were shown to reduce transcriptional activity in vitro (alleles *1D, *1H, *9) (Haberl, M., Et Al, 2005).

Role of dopamine in tobacco addiction

Much of the pleasure derived from smoking tobacco is thought to come from activation of the dopamine system, and in particular the dopamine D2 receptor, in the brain (Noble *et al.*, 1994). Although the exact mechanism by which dopamine exerts its effects is unclear (possible biological mechanisms are reviewed by Munafo *et al.* (Munafo *et al.* 2001)), the body of literature suggests that a lack of dopamine causes a 'reward deficit' whereby people compensate for the deficiency through the use other substances such as alcohol and nicotine (reviewed by Blum *et al.*, 1996).

Genetic variation in the gene encoding DRD2

Approximately 35% of people have a variant version of the gene that codes for the dopamine receptor D2 (DRD2); the receptor thought to be important in the reward pathway. This frequency increases to 45% among Caucasians and is higher still in other ethnic sub-groups. Several studies have shown that the *DRD2 Taq1A* variant is linked to reduced dopamine binding in the brain through decreasing the number (density) of dopamine D2 receptors and decreasing dopamine binding at DRD2 (for example, Jonsson *et al.*, 1999; Thompson *et al.*, 1997). Recent work shows that the DRD2 variant lies in a previously unknown gene (ANKK1) encoding a protein kinase. The variant changes the amino acid composition of the protein that the gene encodes and may affect substrate-binding specificity (Neville et al., 2004).

Several large and well-designed studies have shown that the variant form of the gene is more common in people who regularly smoke tobacco (for example Comings *et al.*, 1996), although the overall effects are small (Systematic meta-analysis: Munafo et al., 2004).

Nicotine replacement appears to be more effective in the short term in people with *DRD2 Taq1A* variant compared to people who have the common version of the gene (Johnstone et al., 2004). It also appears that people with the common version of the gene respond well to bupropion (Zyban) which is the alternative therapy commonly used for smoking cessation (Lerman et al., 2003). Two studies have shown that women with the variant version of the gene are at increased risk of side effects with bupropion (Lerman 2003, Swan 2005).

McKinney et al., (2000) found that allelic variations in another gene involved in dopamine metabolism, dopamine beta hydroxylase gene (DBH), predicted to some degree whether a person was a heavy smoker and how many cigarettes they consumed. More heavy smokers had the DBH 1368A allele when compared to light smokers. This gene seemed to work in the same way as DRD2 predicting who would respond well to nicotine replacement (Johnstone 2004)

What does the DNA test do?

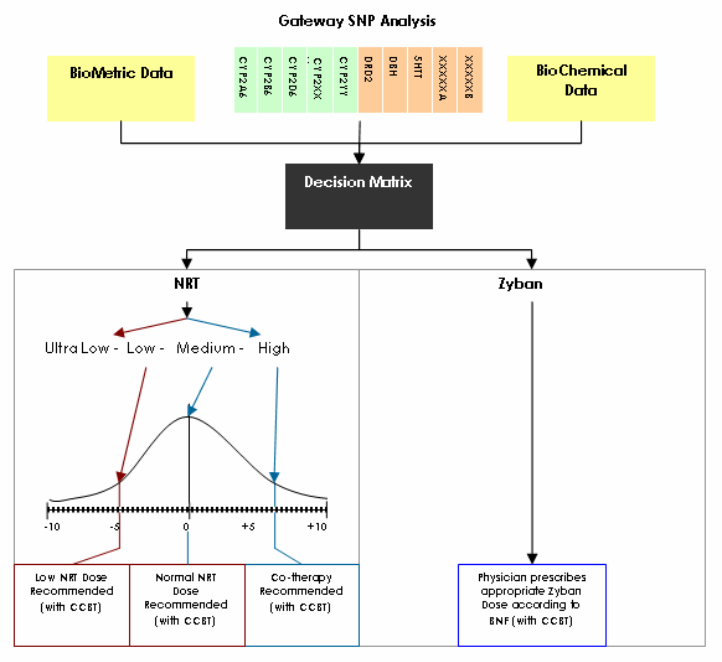
The pharmacogenetic component of the NicoTest™ programme analyses the patient's blood sample for the following gene variants:

- CYP2A6 alleles
  - CYP2A6 Deletion (*4)
  - CYP2A6*2
  - CYP2A6*9B
  - CYP2A6*12B
- DRD2 32806/ANKK1/DRD2 Taq 1a
- DBH1368

The CYP2A6 genotype is used to estimate the rate of nicotine metabolism and thus advise on dose of nicotine replacement.

The DRD2 and DBH information informs choice of therapy (nicotine *v* non-nicotine) on the basis of likely side effects and efficacy. It is important to note that this component of the recommendations is based on the few published studies detailed above and are thus advisory only at this stage.

© g-Nostics Ltd., 2006



Scorpions™ Technology

The NicoTest™ programme uses Scorpions™ technology for sample analysis. Scorpions™ technology is a homogeneous or closed-tube platform for PCR analysis. More information relating to Scorpions™ Technology is available on request.

NicoTest™ Computerised Cognitive Behavioural Therapy

Our online programme delivers a convenient and wide-reaching 'managed care' service for smokers endorsed by both the **American Cancer Society** and the **Canadian Cancer Society**.

Your Patient's smoking History

The NicoTest™ programme collects data for Primary Care Trusts (PCTs). This information is entered by the patient themselves thereby reducing the workload for the medical professional.

For example in Milestone 1 of the NicoTest™ *Flight to Freedom* the following questions are asked:

The patient's smoking history

- The number of cigarettes that the patient smokes
- Patient's year of birth
- Number of years that the patient has smoked
- The amount that the patient spends on smoking per day
- Whether the patient co-habits with other smokers
- The patient's city or town of residence
- The patients country of residence
- The patients sex
  - If the patient is female then is the patient
    - Pregnant
    - Brestfeeding
- The patients email address
- The number of times that the patient has attempted to quit
- The methods that the patient used in previous quit attempt
  - No NRT or Prescription Medication
    - Cold Turkey
  - Over-the-Counter (Non-Prescription) Products:
    - Nicotinell Patch
    - NicQuitin CQ Patch
    - Nicotinell Gum
    - NicQuitin CQ Gum
    - Nicotinell Lozenge
    - NicQuitin CQ Lozenge
    - Nicorette Inhaler
    - Boots Patch
    - Nicorette Patch
    - Boots Gum
    - Nicorette Nasal Spray
    - Boots Lozenge
    - Nicorette Gum
  - Prescription Products:
    - Zyban
    - Allegron
    - Clonidine
    - Catapress
    - Dixarit
    - Varenicline
    - Rimonobant
    - Another Prescription Medication
- Patient's height (BMI)
- Patient's weight (BMI)
- Patients ethnicity
  - White
    - British
    - Irish
    - Any other White background
    - Any other background
    - b. Black or Black British
    - Caribbean
    - African
    - Any other Black background
  - c. Asian or Asian British
    - Indian
    - Pakistani
    - Bangladeshi
    - Any other Asian background
  - d. Mixed
    - White and Black Caribbean
    - White and Black African
    - White and Asian
    - Any other mixed background
  - e. Other ethnic groups
    - Chinese
    - Japanese
    - Any other ethnic group
- Patient's marital status
- Patient's employment status
- Patient's level of education

NicoTest™ Stages of Change model

NicoTest™ CCBT consists of a personalised 6-Step behaviour modification program based on the Stages of Change model. The exercises in the program help patients analyse their past smoking habit, modify their behaviour and create a reward-based plan. After users set their quit date they return to their diary to record their progress. The diary assesses and displays the gains they have made from quitting, including smoke-free days, number of cigarettes not smoked, money saved as well as life year's gained as a result of a new non-smoking lifestyle.

© g-Nostics Ltd., 2006

NicoTest™

Computerise decision support enables tailored dosing

A review conducted by Walton et al (2001) concludes that "computer support for drug dosage is potentially an effective way of changing clinical practice and may bring benefits to patients. Unaided clinicians tended to use lower loading, maintenance and total doses, than when computer support was available. Lower doses lead to lower blood levels and often to sub-optimal therapeutic effects. Although doses with computer support tended to be higher than those used by unaided doctors, toxic drug levels and adverse effects were significantly reduced. This suggests that the computers helped doctors to tailor the dose of the drug more accurately to the individual patient. Higher doses with computer support may lead to more rapid therapeutic control, bringing benefits for patients and reducing the time spent in hospital" (Walton, RW et al (2001). Computerised advice on drug dosage to improve prescribing practice. The Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.:002894. DOI: 10.1002/14651858.CD00894. p.5).

Computerised cognitive behavioural therapy helps smokers quit

Cognitive Behavioural Therapy (CBT) and Online Managed Care provides a high-reach low-cost solution for managed care at a primary level. "We find that managed care has made significant progress—and that opportunity remains", (Cutler, 2003).

Farvolden (2003) found that web-based collaborative disease managements systems and behaviour modification have the potential to improve patient outcomes by providing increased support at the population level.

The benefits of the Internet, however, enable high-reach, low-cost personalised solution. Three of the key features of the Internet and web-based management can be characterized as follows:

- **Data and Tracking**: the ability to save and retrieve patient data at all stages of the disease management cycle, i.e. diagnosis, treatment, progress monitoring
- **Content Customization**: the ability to represent the treatment process in a comprehensive and customized graphic format, i.e. the use of web browsers, graphic representation of stepped models of care
- **Interaction**: the ability for patients to communicate directly with their primary care physician and other patients who are progressing through the same methods of treatment , i.e. via email, moderated support groups, instant messaging technology, counselling sessions, etc.

Personalised treatment can improve success rates

"Web-based Support Groups for smoking cessation offer high-reach and personalised support for smokers at low cost per patient" (Fournier, 2004). Computerised tailoring of smoking cessation materials and advice has been investigated (e.g. Strecher et al., 1994; Disjkstra & De Vries, 1999; Strecher ,1999), generally indicating positive effects among moderate to light smokers. Such tailoring is dependent on the conceptual framework adopted, and is typically predicated on the Transtheoretical Model of behaviour change, so that readiness to change is the central variable used to tailor smoking cessation messages (Dijkstra et al., 1999).

The Addressing Tobacco in Managed Care (ATMC) initiative is based on the understanding that managed healthcare plans—which have information systems, defined populations, and other infrastructure to improve patient care—are well suited to implement, evaluate, and institutionalize tobacco control interventions. The results of the 2000 ATMC survey suggest that health plans have demonstrated great progress in their efforts to address tobacco use as one of the leading causes of preventable death and illness.

Jean-Francios Etter found that new computer-tailored cessation programs were effective in increasing cessation rates, "because it can reach large numbers of smokers, this program can substantially contribute to disease prevention at a population level" (Etter, J., Perneger, T., 2001.

INDEPENDENT ACADEMIC AND SCIENTIFIC COMMENTS ON THE NICOTEST™

Professor J Gordon McVie, MD, FRCP, FRCPS ,FRCSE, FMedSci, DSc(Hon)

"Cancer exists in at least 200 forms, each genetically different from one another. There was never going to be a "One Size Fits All" for cancer treatment, nor cancer prevention. So it's not surprising that different approaches need to be tailor made to each individual at high risk of cancer. Add to this the variation in genetic predisposition to handling addictive products and other drugs, and the common sense behind this new test becomes blindingly obvious.

I've watched this genetic approach to cigarette withdrawal all the way from the research in ICRF labs through to the setting up of the company, to the launch of the product today. This is a model of how we should exploit basic research in the prevention of cancer."

Professor Gordon McVie is a leading international authority in the research and treatment of cancer. For the past seven years he has served the US Journal of the National Cancer Institute as its European editor.

He is currently a Director of the European Institute of Oncology, Milan. He is visiting professor at Glasgow University in Scotland and honorary Consultant in medical oncology at the Welsh Cancer Institute, Cardiff.

Previously Professor McVie was Chief Executive of the Cancer Research Campaign. Throughout the Eighties, he was clinical research director at the National Cancer Institute of the Netherlands. He was made a Fellow of the Royal College of Surgeons of Edinburgh in 2003.

Michael Thick:

"This approach to treating addiction to smoking is long overdue, and it is particularly pleasing that the power of these genetic technologies has become available to the public. Everyone should have the opportunity to understand how treatments can be tailored to them as individuals, and therefore make an informed choice about what will suit them best. Smoking causes very considerable illness and death, and this service will be a significant tool to help those wishing to give up."

Michael Thick is the National Medical Director, Choose & Book Programme – National Programme for Information Technology at the Department of Health. Thick has also been a visiting Professor for the National Heart & Lung Institute, Imperial College and a Consultant Transplant Surgeon at Freeman Hospital.

Peter Selby

"For the first time, smokers will have the opportunity to use a truly biopsychosocial approach to the number one addiction in society. This practical application of genetics for the treatment of a clinical

© g-Nostics Ltd., 2006

condition that affects so many people is revolutionary in the field of medicine."

Associate Professor Peter Selby is the Clinical Director, Addictions Program, Center for Addiction and Mental Health at the University of Toronto.

Professor Jed E. Rose, Ph.D.

"If realized, the promise of individualizing smoking cessation treatment based on a genetic predictor would be an important advance".

Professor Rose is the Director of the Centre for Nicotine and Smoking Cessation Research at Duke University, USA. He was the co-inventor of the nicotine patch and has been involved at the forefront of nicotine research for almost two decades.

INDEPENDENTLY VALIDATED CLAIMS

Over 109 evidence-based peer-reviewed papers were independently evaluated prior to the availability of Nicotest™. Whilst each of the process components has been separately validated the Nicotest™ will benefit from the current Phase IV style study to monitor progress in real-time. We have also invited eminent academics in this arena to review our data for their comment. Based on this review the following claims can be supported:

1. Increase quit rates by using a structured smoking cessation programme

- Structured smoking cessation programmes have been shown to improve success rates

There is extensive evidence that behavioural treatment improves global long-term quit rates. The most widely studied behavioural intervention is adjunctive advice and instruction from a health care professional. Other programmes follow the principles of behaviour modification more closely, such as operant conditioning. Cinciripini et al., (1994) report that scheduled smoking (which removes the association between smoking urges and reinforcement) is a useful addition to multi-component treatment programmes. Cognitive-behavioural programmes to manage mood and withdrawal symptoms have also been shown to be effective

References: Cornuz et al., 1997; Lifrak et al., 1997; Hall et al., 1994; Cinciripini et al., 1996; Cinciripini et al., 1994; Marlow and Stoller, 2003; Fortmann and Killen, 1995; Wright et al., 1996; Glasgow et al., 2000

2. Increase quit rates by taking the right medication at the right dose

- Stratification by genotype identifies individuals who will respond well to nicotine replacement or bupropion therapy

References: Learman et al., 2003; Swan et al 2004, Johnstone 2004

- Stratification by genotype enables rate of metabolism of nicotine to be estimated

Genes that influence metabolic enzymes responsible for the metabolism of nicotine to cotinine have been extensively researched in relation to smoking behaviour, and there is evidence that they predict, for example, levels of cigarette consumption. There is good evidence for a functional effect of CYP2A6 genotype on nicotine metabolism (e.g. Zhang et al., 2002).

Pianezza et al. (1998) first reported a lower incidence of CYP2A6 null alleles among tobacco dependent individuals compared to non-dependent individuals. Despite subsequent conflicting results (reviewed in Oscarson, 2001), CYP2A6 genotype remains a strong candidate gene for smoking behaviour. Several studies have reported an association with smoking behaviour (typically level of dependence or cigarette consumption) (e.g. Tyndale et al., 1999; Rao et al., 2000; Iwahashi et al., 2004), although there have also been negative reports (e.g. Ando et al., 2003). The evidence from a recent meta-analysis (Munafò et al., 2004) indicated that CYP2A6 genotype may be associated with likelihood of being a former smoker. Inhibition of CYP2A6 activity in vivo has also been shown to alter smoking behaviour (e.g. Tyndale & Sellers, 2001; Sellers et al., 2003).

Taken together, this evidence suggests that CYP2A6 genotype is likely to be associated with nicotine metabolism and, consequently, smoking behaviour (most probably consumption), but that this association may vary across ethnic groups in whom the prevalence of null alleles varies considerably.

References: Zhang et al., 2002; Pianezza et al., 1998; Tyndale et al., 1999; Rao et al., 2000; Iwashi et al., 2004; Ando et al., 2003; Munafo et al., 2004; Tyndale and Sellers, 2001; Sellers et al., 2003

- The FTND allows a person's degree of dependence on nicotine to be estimated

The six-item Fagerström Test for Nicotine Dependence (FTND) is a reliable and valid self-reported measure of nicotine dependence (Fagerström et al., 1990). This is the most widely used measure of nicotine dependence (Benowitz, 1999), and has been reported to predict likelihood of smoking cessation success (Balfour et al., 2000), although only two items strongly predict likelihood of cessation (numbers of cigarettes per day, and time to first cigarette smoked).

The FTND has also been used to identify sub-types of dependent smokers, and a cut-off score of 5 generally is recognized to indicate dependence (Lesch et al., 2004). Other measures of nicotine dependence, such as DSM-IV criteria, may underestimate the prevalence of nicotine addiction in the population (Benowitz, 1999).

References: Fagerström et al., 1990; Benowitz, 1999; Balfour et al., 2000; Etter et al., 1999; Lesch et al., 2004

- High-dose therapy of NRT improves quit rates for heavier smokers

High dose nicotine replacement therapy may improve success rates in heavy or highly dependent smokers. In addition to this tailoring nicotine replacement therapy dose based on cigarette consumption or FTND score enables lighter smokers to minimize the cost associated with nicotine replacement therapy.

References: Gorsline et al., 1991; Bannon et al., 1989; Hughes et al., 1990; Dale et al., 1995; Tonnesen et al., 1999; Jorenby et al., 1995; Fredrickson et al., 1995; Benowitz et al., 1998; Hurt et al., 1993

3. Increase quit rates by using professional support during the quit

- Professional support during a smoking cessation attempt has been shown to improve success rates

Increasing the intensity of professional intervention has been widely reported to improve smoking cessation rates. The usual means by which the level of intervention or support is increased is by telephone contact following the initial intervention.

References: Miller et al., 1997; Alterman et al., 2001; Reid et al., 1999

4. Increase quit rates by combining medication and online support

- Nicotine replacement therapy has been demonstrated to be a safe and effective aid to smoking cessation
- Online support and medication increased the success rate from 4.5% for 'cold turkey' up to 18% for a randomised sample using a combined approach

References: West, R., McNeil, A. (2000)

5. Increase quit rates with Personalised Treatment

- Personalised treatment based on a person's readiness to stop smoking has been shown to improve success rates

References: Mogielnicki et al., (1986); Owens et al., (1989); Rimer and Orleans, 1994; Orleans, 2000; Secker-Walker et al., 1994; Bane et al., 1999; Strecher et al., 2000; Disjkstra and De Vriew, 1999; Borland et al., 2004; Mermelstein et al., 2003

We are constantly collecting data to refine and improve our tailoring of treatment to individuals, based on age, sex, lifestyle and ethnicity. We expect to issue a broader range of treatment reports to reflect this continuous improvement as we move forward.

REFERENCES

Alterman AI et al. (2001). Short- and long-term smoking cessation for three levels of intensity of behavioral treatment. Psychology of Addictive Behaviours, 15, 261-264.

Bane CM et al. (1999). Development of a pregnancy-tailored decisional balance measure for smoking cessation. Addictive Behaviors, 24, 795-799.

© g-Nostics Ltd., 2006

NicoTest™

Bannon YB et al. (1989). Transdermal delivery of nicotine in normal human volunteers: a single dose and multiple dose study. European Journal of Clinical Pharmacology, 37, 285-290.

Benowitz NL et al. (1998). Suppression of nicotine intake during ad libitum smoking by high-dose transdermal nicotine. Journal of Pharmacology and Experimental Therapeutics, 287, 958-962.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, Comings DE. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med 1996;89(7):396-400.

Cinciripini PM et al. (1994). An evaluation of a multicomponent treatment program involving scheduled smoking and relapse prevention procedures: initial findings. Addictive Behaviors, 19, 13-22.

Cinciripini PM et al. (1996). Behavior therapy and the transdermal nicotine patch: effects on cessation outcome, affect, and coping. Journal of Consulting and Clinical Psychology, 64, 314-323.

Comings DE, Ferry L, Bradshaw-Robinson S, Burchette R, Chiu C, Muhleman D. The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. Pharmacogenetics 1996;6(1):73-9.

Cornuz J et al. (1997). Smoking cessation counseling by residents in an outpatient clinic. Preventive Medicine, 26, 292-296.

Cutler, C., Preventative medicine in managed care, JUNE 25, 2002, VOL. 3, NO. 3

Dale LC et al. (1995). High-dose nicotine patch therapy: percentage of replacement and smoking cessation. Journal of the American Medical Association, 274, 1353-1358.

Dijkstra A & De Vries H (1999). The development of computer-generated tailored interventions. Patient Education and Counseling, 36, 193-203.

Dijkstra A et al. (1999). Targeting smokers with low readiness to change with tailored and nontailored self-help materials. Preventive Medicine, 28, 203-211.

Etter JF & Perneger TV (2001). Effectiveness of a computer-tailored smoking cessation program: a randomized trial. Archives of Internal Medicine, 161, 2596-2601.

Farvolden, P and Mierlo, T, (2003). Web-based collaborative disease management and health behaviour change [Available at http://www.v-cc.com/research/]

Fortmann SP & Killen JD (1995). Nicotine gum and self-help behavioral treatment for smoking relapse prevention: results from a trial using population-based recruitment. Journal of Consulting and Clinical Psychology, 63, 460-468.

Fournier, R., (2004). NRT and Buproprian usage amoung users of a web-based smoking cessation support group [Available from: http://www.v-cc.com/research/]

Fredrickson PA et al. (1995). High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. Psychopharmacology, 122, 215-222.

Gorsline J et al. (1991). Nicotine dose relationship for Nicoderm at steady state. Pharmaceutical Research, 10, S299.

Haberl, M., Et Al, (2005). Three haplotypes associated with CYP2A6 phenotypes in Caucasians. Pharmacogenetics and Genomics 2005, 15:609–624

Hall SM et al. (1994). Cognitive-behavioral intervention increases abstinence rates for depressive-history smokers. Journal of Consulting and Clinical Psychology, 62, 141-146.

Hughes JR et al. (1990). Effect of dose on nicotines reinforcing, withdrawal-suppression and self-reported effects. Journal of Pharmacology and Experimental Therapeutics, 252, 1175-1183.

Hurt RD et al. (1993). Serum nicotine and cotinine levels during patch therapy. Clinical Pharmacology and Therapeutics, 54, 98-106.

Johnstone EC, Yudkin PL, Hey K, Roberts SJ, Welch SJ, Murphy MF, Griffiths SE, Walton RT. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. Pharmacogenetics 2004;14(2):83-90.

Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol Psychiatry 1999;4(3):290-6.

Jorenby DE et al. (1995). Varying nicotine patch dose and type of smoking cessation counseling. Journal of the American Medical Association, 274, 1347-1352.

Lancaster T, Stead LF. Self-help interventions for smoking cessation. Cochrane Database Syst Rev 2002(3):CD001118.

Lerman C, Shields PG, Wileyto EP, Audrain J, Hawk LH, Jr., Pinto A, Kucharski S, Krishnan S, Niaura R, Epstein LH. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. Health Psychol 2003;22(5):541-8.

Lerman et al. (2002). Pharmacogenetic investigation of smoking cessation treatment. Pharmacogenetics, 12, 627-634.

Lifrak P et al. (1997). Results of two levels of adjunctive treatment used with the nicotine patch. American Journal of Addiction, 6, 93-98.

Marlow SP & Stoller JK (2003). Smoking cessation. Respiratory Care, 48, 1238-1254.

McKinney EF, Walton RT, Yudkin P, Fuller A, Haldar NA, Mant D, Murphy M, Welsh KI, Marshall SE. Association between polymorphisms in dopamine metabolic enzymes and tobacco consumption in smokers. Pharmacogenetics 2000;10(6):483-91.

Mermelstein R et al. (2003). Extended telephone counseling for smoking cessation: does content matter? Journal of Consulting and Clinical Psychology, 71, 565-574.

Miller NH et al. (1997). Smoking cessation in hospitalized patients. Results of a randomized trial. Archives of Internal Medicine, 157, 409-415.

Mogielnicki RP et al. (1986). Tailored media can enhance the success of smoking cessation clinics. Journal of Behavioral Medicine, 9, 141-161.

Munafò et al. (2004). The genetic basis for smoking behavior: A systematic review and meta-analysis. Nicotine and Tobacco Research, 6, 583-597.

Munafo M, Johnstone E, Murphy M, Walton R. New directions in the genetic mechanisms underlying nicotine addiction. Addict Biol 2001;6(2):109-117.

Munafo' M, Johnstone E, Welsh K, Walton R. Association between the DRD2 gene TAq1A polymorphism and alcohol consumption in social drinkers (in press). The Pharmacogenomics Journal 2004.

Munafo MR, Clark TG, Moore LR, Payne E, Walton R, Flint J. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. Mol Psychiatry 2003;8(5):471-84.

Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat 2004;23(6):540-5.

Noble EP, St. Jeor ST, Ritchie T, Syndulko K, St. Jeor SC, Fitch RJ, Brunner RL, Sparkes RS. D2 dopamine receptor gene and cigarette smoking: a reward gene? Med Hypotheses 1994;42(4):257-60.

Orleans CT & Fishman J (2000). Tailored communications for smoking cessation. Introduction. Tobacco Control, 9, I49.

Orleans CT et al. (2000). Computer tailored intervention for older smokers using transdermal nicotine. Tobacco Control. 9, I53.

Owens N et al. (1989). Smoking cessation by mail: a comparison of standard and personalized correspondence course formats. Addictive Behaviors, 14, 355-363.

Reid RD et al. (1999). Is telephone counselling a useful addition to physician advice and nicotine replacement therapy in helping patients to stop smoking? A randomized controlled trial. Canadian Medical Association Journal, 160, 1577-1581.

Rimer BK & Orleans CT (1994). Tailoring smoking cessation for older adults. Cancer, 74, 2051-2054.

Secker-Walker RH et al. (1994). Individualized smoking cessation counseling during prenatal and early postnatal care. American Journal of Obstetrics and Gynecology, 171, 1347-1355.

Strecher VJ (1999). Computer-tailored smoking cessation materials: a review and discussion. Patient Education and Counseling, 36, 107-117.

Swan GE, Valdes AM, Ring HZ, Khroyan TV, Jack LM, Ton CC, Curry SJ, McAfee T. Dopamine receptor DRD2 genotype and smoking cessation outcome following treatment with bupropion SR. Pharmacogenomics J 2004.

Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry EK, Morris CM, Perry RH, Ferrier IN, Court JA. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 1997;7(6):479-84.

Tonnesen P et al. (1999). Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE study. European Respiratory Journal, 13, 238-246.

Walton R, Dovey S, Harvey E, Freemantle N. Computer support for determining drug dose: systematic review and meta- analysis BMJ 1999;318(7189):984-90.

Walton RT, Harvey E, Dovey S, Freemantle N. Computerised advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev 2001(1):CD002894.

Walton, RW et al (2001). Computerised advice on drug dosage to improve prescribing practice. The Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.:002894. DOI: 10.1002/14651858.CD00894

Wright LN (1996). Statewide assessment of a behavioral intervention to reduce cigarette smoking by pregnant women. American Journal of Obstetrics and Gynecology, 175, 283-287

Yamano S, Tatsuno J, Gonzalez FJ. The CYP2A3 gene product catalyzes coumarin 7-hydroxylation in human liver microsomes. Biochemistry 1990;29(5):1322-9.

© g-Nostics Ltd., 2006

Yudkin P, Munafo M, Hey K, Roberts S, Welch S, Johnstone E, Murphy M, Griffiths S, Walton R. Effectiveness of nicotine patches in relation to genotype in women versus men: randomised controlled trial. BMJ 2004;328(7446):989-90.

Zabetian, C. P.; Anderson, G. M.; Buxbaum, S. G.; Elston, R. C.; Ichinose, H.; Nagatsu, T.; Kim, K.-S.; Kim, C.-H.; Malison, R. T.; Gelernter, J.; Cubells, J. F.(2001). A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: evidence for a major functional polymorphism at the DBH locus. Am. J. Hum. Genet. 68: 515-522, 2001. PubMed ID : 11170900.

© g-Nostics Ltd., 2006