

Three reasons not to buy the NicoTest™ genetic test

GeneWatch UK

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What is the NicoTest™?

NicoTest is a new genetic test kit being marketed directly to the public via the internet (www.nicotest.com). It is marketed by a company called g-Nostics Ltd which hopes to sell it more widely in the future, both “over the counter” and via doctors in the National Health Service. G-Nostics is a “spin out” company from Oxford University. The university is a shareholder in the company and the test is based on research by Dr Robert Walton in the university’s Department of Clinical Pharmacology¹. Dr Walton is Chief Scientific Officer, Lead Inventor and co-founder of the company².

NicoTest is a smoking cessation programme, which includes three things:

1. A questionnaire and DNA test which the company claims will identify which smokers are more likely to respond to nicotine replacement therapy (nicotine patches, gum and inhalers) and less likely to respond to drugs such as bupropion (Zyban) when they try to quit smoking;
2. A second DNA test which the company claims gives the customer’s metabolic profile (how their body responds to nicotine) and therefore how much nicotine replacement to take;
3. A programme of support to quit, including email, chat rooms and a computer programme (based on cognitive behavioural therapy).

The test costs £94.99 and involves sending a drop of blood to the company by post.

Which genes are tested?

The first genetic test involves a gene which the company claims predisposes people to nicotine addiction. Although this gene is not named on the website, it is clear from the references given that it is a gene known as the ‘dopamine D2 receptor gene’, DRD2. A common variation in this gene is claimed to relate to how useful people find nicotine patches when they try to stop smoking. People with the ‘addiction gene’ supposedly find nicotine patches more useful than people without it, but people without the ‘addiction gene’ supposedly find the drug bupropion (better known by its trade name, Zyban) more useful.

The second genetic test gives a ‘metabolic profile’ and is used to advise how much nicotine replacement to take. The main gene thought to be involved in nicotine metabolism is called CYP2A6.

**In GeneWatch’s view this genetic test is, at best, a waste of money and could also be misleading and potentially harmful to health.
We recommend that you do not take this test.**

The claims made for this genetic test are based on partial and misleading evidence. For example, the claimed “addiction gene” included in the test does not have a statistically significant association with nicotine addiction.

GeneWatch believes that an independent regulator should be set up to assess all genetic tests before they are sold. We also think that genetic tests should not be marketed directly to the public, but only via medical professionals who can ensure that they are properly interpreted.

The following is a summary of our concerns about the NicoTest™.

1. Poor and selective scientific evidence.

1.1 The claimed nicotine “addiction gene” does not have a statistically significant association with smoking.

The NicoTest website claims that its first genetic test identifies people born with “a *gene predisposing them to nicotine addiction*” (these are the people advised to use nicotine replacement therapy when they try to stop smoking). In fact the statistical link between this gene (DRD2) and nicotine addiction is disputed – some studies have found a link but others have not. A recent study has attempted to combine the results of all the research on the DRD2 gene. It found that the association between the gene and smoking behaviour (the likelihood of starting, continuing and quitting smoking) was not statistically significant when the most sophisticated analysis was used³. This means the link remains at best uncertain and may not exist at all.

The most recent study in the UK concludes that inherited genetic variations in DRD2 “*have little or no effect on an individual’s smoking behaviour*”⁴ and states this finding is consistent with the only earlier study done in the UK. G-Nostics Ltd must know about these studies because its Chief Scientific Officer, Lead Inventor and Co-Founder (Dr Robert Walton) is one of the authors on these scientific papers.

<p>It is wrong to tell people that they have a “nicotine addiction gene” when the evidence for this claim does not meet accepted scientific standards.</p>

1.2 Published scientific evidence suggests that the first DNA test may be no use at all for deciding which treatment best helps men to quit.

The “FAQs” section of NicoTest™ website cites one journal paper which it says shows that its DNA test can identify people who are more likely to respond to nicotine replacement therapy (NRT)⁵ – these are the people with the so-called addiction gene (the rarer form of the DRD2 gene, which about 35% of people have). The website does not cite a more recent paper in the British Medical Journal, which repeats the same study looking at differences between men and women with the DRD2 gene⁶. This study concludes: “*In women the effectiveness of nicotine patches seems to be related to genotype [genetic makeup]...No significant relationship between genotype and patch effectiveness was seen for men*”. Again, Dr Walton is an author on both these scientific papers.

The same section of the website cites a different scientific paper which it says shows its DNA test will identify people less likely to respond to bupropion (Zyban)⁷. This paper looks for links between different variations in the DRD2 gene and success in quitting smoking for people taking this drug. It also concludes that: “*Significant associations or trends were not observed in men*”. When the results for men and women were combined together, the effect of the gene on response to Zyban was not statistically

significant. Another study (not cited on the website) has also found that the effect of the DRD2 gene on quitting smoking using Zyban was not significant when men and women were combined together⁸.

The website does not mention evidence that its genetic test is not likely to be useful for men. This is a particularly serious omission because more men than women smoke.

1.3 The evidence that the first DNA test is useful to women is limited and partial.

The evidence that the first DNA test is useful to identify who responds best to nicotine patches is based on a single study of 1625 people, 752 of whom then had the genetic test⁵. This scientific paper does not conclude that people should have a genetic test before using nicotine patches – it concludes that more research is needed. Although it found a link between genetic makeup and the effectiveness of nicotine patches (for a group of 445 women and 307 men combined) this was only observed in the short term. In fact, the link between the claimed “nicotine addiction gene” and the effectiveness of nicotine patches was only statistically significant in the first week. A slightly longer effect (up to 12 weeks) was observed when another gene (called DBH) was added to the test and the researchers looked at the effect of the two genes together. The study says: “*There were no associations between genotype and patch effectiveness beyond 12 weeks*”.

Because the effect of the genetic difference was small, a further scientific paper based on the same study looked at the differences between men and women⁶. In this study, nicotine patches helped women with the ‘good responder’ gene (the so-called ‘addiction gene’) to quit, even in the longer term (up to 8 years of not smoking) but they did not help men with this gene to quit. If this conclusion is correct, it means this single gene alone does not determine a person’s response to the patches – there must be other factors involved, or the effect in women may have occurred by chance or for some other unknown reason. The study says: “*In women the effectiveness of nicotine patches seems to be related to genotype*” and the scientists suggest a possible explanation - that nicotine replacement therapy may be subject to different genetic influences in men and women. This theory has not been tested by further research and there might be other explanations for this finding.

The evidence that the first DNA test is useful to decide who should use bupropion (Zyban) is even weaker⁷. In this case a single study found no differences in men and only small differences in women who had a different genetic makeup. This study concluded that women’s response to Zyban “*may be partially due*” to these genetic differences. The authors also admit that the interactions between several different genes are likely to be important and it is “*quite probable*” that the study is not large enough to identify these effects. A different study (not cited on the website) found that the DRD2 gene might be important, but only when combined with the effect of another gene⁸. Again, much more research is needed to draw definite conclusions.

Scientists are now finding that most studies linking genes with diseases⁹ or with behaviour (including addiction)¹⁰ are not confirmed when the studies are repeated. Usually the gene turns out to be much less important than first thought. Predicting response to medicines from a genetic test may be easier than predicting disease or behaviour, but is still very complex¹¹. These problems need to be resolved before genetic tests are sold. When there are many different possible ways that genes could

work (for example: lots of different genes; lots of other factors; the possibility that different factors are important in men and women) very large and careful studies are needed to tell which explanation is correct.

Selling a genetic test based on a single study is irresponsible because the results of this kind of study usually turn out to be misleading when more research is done.

1.4 There is no evidence provided for the second DNA test.

The “FAQs” section of the website says that a second DNA test will give the user’s “metabolic profile” for nicotine and therefore how much nicotine replacement to take. It says: *"This is much better than trial and error!"*. But the website gives no scientific reference for its claim and later admits: *"Until we collect the figures it is very difficult to estimate the benefit in terms of quitting"*. Taking this second DNA test therefore amounts to paying to take part in a research project. The metabolism of nicotine is complex¹² and it is unlikely that a single genetic test can replace the need for trial and error. This is because many different biological and other factors (such as social and psychological factors) are likely to be involved¹³. Scientists do not yet know if it will be possible to predict the best dose of nicotine replacement therapy for an individual.

The NicoTest website does not say which genes will be tested for the ‘metabolic profile’ but a gene called CYP2A6 is the most likely one to be included. This gene makes an enzyme that metabolises nicotine (it breaks it down into a different chemical). There is some evidence that different variations in this gene are linked with different likelihoods of successfully quitting smoking, but this evidence is not conclusive because there are some errors in one of the studies that has been done³. The genetic variations in CYP2A6 that might be linked with success in quitting are also rather rare in white people in Britain.

Taking the second genetic test amounts to paying to take part in a research project. No evidence yet exists that using this test to choose the dose of nicotine replacement therapy is better than trial and error.

1.5 NicoTest’s claims about success rates are selective and misleading.

NicoTest quotes success rates for quitting smoking on its website. Some relate to people who have the claimed ‘addiction gene’ and others to people who do not. Some are for people who have used Zyban or nicotine patches and others are for people who have not. Some are short-term success rates (people who have abstained from smoking for only one week) and others are long-term (people who have not smoked for 8 years). In many cases the website makes false comparisons and fails to make clear the limitations of the evidence.

The NicoTest™ website says: *"Analysis of clinical trials eight years afterwards have shown that up to 40 percent of smokers with the ‘addiction gene’ can successfully give up if they use specific and appropriate nicotine replacement therapy (NRT), while around 20 percent who don’t have it can still succeed with relevant and appropriate treatment. This compares to around 4 percent for those who don’t use NRT or follow appropriate treatment"*¹⁴. Elsewhere on the website it is claimed that if this second group

of people (those without the ‘addiction gene’) try bupropion (Zyban) their success rate can increase from 20% to “*about the same as for nicotine replacement therapy*” (40%)¹⁵.

These claims are seriously misleading because the clinical trial that looked at smokers “eight years afterwards” did not show success rates of up to 40% after eight years⁶. It showed success rates this high only for the shortest time period (after one week)⁵. The FAQs section of the website refers to success rates after one week, but the front page implies this is the eight year figure. The 4% success rate quoted for people who do not use any treatment is an eight year figure – so it is wrong to compare it with the one week figures for people who use treatment.

This means, firstly, that the effects of treatment (with nicotine patches or with Zyban) have been greatly exaggerated. For the study referred to on the NicoTest website, success rates after eight years were 5% (5.9% with nicotine patches and 4.3% without) and after one year were 9.4% (11.2% with patches and 7.7% without)¹⁶. Other researchers have also looked at success rates after one year. They have found that smokers who use nicotine patches to quit typically have success rates after one year of about 14% compared to about 8% without (combining the results of 33 studies), and those who use bupropion (Zyban) have success rates of about 17% compared to about 10% without (combining the results of 7 studies)¹⁷. Adding counselling can increase these success rates further¹⁸. This means that treatment with nicotine patches or with Zyban does help people to quit smoking, but not to the extent that is implied on the NicoTest website. The statement (made in the FAQs section of the website) that of the people who stop smoking at one week “*about 50%*” will be smoke free after 8 years is also incorrect – this applies to smokers who have stopped smoking for one year (not just for one week)¹⁶.

Secondly, most of these studies do not include any assessment of whether taking a genetic test will help or not – it could improve or worsen these success rates, or simply make no difference. The conclusion that the genetic test will help smokers to give up is based only on the two studies cited by the company (one study for nicotine patches and one study for Zyban): this conclusion is likely to be untrue for men and may be unreliable for women based on this published evidence. The figures quoted in the FAQs section of the website are based on the effect of using nicotine patches after one week only: significant differences between those with the “addiction gene” and those without were not seen after longer time periods except when men were excluded from the study.

The one week effect is also smaller than implied on the website (which wrongly compares a 40% success rate for those with the “addiction gene” to a 20% success rate for those without – this figure should be 34%). These one week success rates are also biased because the people who agreed to take part in this part of the study were more likely to quit than those who refused^{16,6}. This means that both the 40% and 34% figures may be misleading (they are probably too high).

The difference in the effectiveness of nicotine patches after only one week (between those with the “addiction” gene and those without) is statistically significant, so it may be a real effect⁵. But it was only a short-term effect observed in a single study. For a population that is half men and half women, taking the genetic test does not help to improve success rates for either nicotine patches or Zyban over the longer term.

The website gives misleading figures for success with treatment – it compares short-term success in stopping smoking for people given treatment to long-term

success rates without treatment. This is a false comparison which exaggerates the benefits of treatment. For the genetic test, the website uses figures from only the first week of a single eight year study and also exaggerates the difference between smokers with and without the claimed “addiction gene”. There is no evidence that the gene test makes any difference to success rates in the longer term, except perhaps in women.

1.6 Some people could be misled by this advice.

Most people who take the NicoTest™ will not succeed in stopping smoking permanently. But some people might be persuaded by their genetic test results that it is not worth trying either nicotine patches or Zyban in the future because these treatments will not work for them. This conclusion would be wrong in many cases and might lead to some people continuing to smoke who might otherwise be helped to quit.

Telling people they have a “nicotine addiction gene” when the link to smoking behaviour is not statistically significant is wrong. But more research is also needed to find out whether this kind of information really helps people to quit. A possible danger is that people could become fatalistic and believe that their addiction to tobacco is genetic and therefore too hard to beat. One study has found that learning of a genetic predisposition to nicotine dependence may increase desire for pharmacological cessation methods (such as nicotine patches or Zyban), but may undermine the perceived importance of willpower in stopping smoking¹⁹. Again, more research is needed.

The effect of misleading genetic information on smokers’ future attempts to quit is currently unknown. However, it is possible that misleading information could be harmful to their health by dissuading them from trying other ways to quit.

Taking the NicoTest could mislead smokers because they may be given wrong advice about which smoking cessation method will work best for them. Misleading information about genes and nicotine addiction could potentially harm health if it affects future attempts to quit.

2. The scientific evidence for the test has not been independently assessed.

The company claims that it operates “*within a regulated environment*”. In fact, regulation of genetic tests is extremely limited. There is no independent assessment of whether or not the gene tested actually predisposes people to nicotine addiction, or whether the test is useful to help choose the best treatment. The “CE mark” and laboratory accreditation referred to on the website involves, at most, an independent check of whether the company has tested the gene that it says it has and found the right genetic variation (DNA sequence). It does not involve any independent check of whether this gene is linked to nicotine addiction or success in using nicotine patches or Zyban.

G-Nostics is a “spin out” company from Oxford University and the university and Oxford Capital Partners are its shareholders²⁰. £4 million has been invested in the company by Oxford University, Oxford Capital Partners and the management team themselves¹⁵. G-Nostics Ltd’s scientific officer is also its lead inventor and co-founder and is a co-author on many of the relevant scientific papers. There is a clear conflict of interest between his

role in promoting a commercial product and at the same time providing and interpreting the evidence given to G-Nostics' customers.

3. The information given to potential customers is incomplete and raises significant ethical concerns.

3.1 Possible links with other conditions

The claimed 'addiction gene' (DRD2) has also been linked with alcoholism, although this link is also far from certain and could be incorrect. Because dopamine is an important chemical in the brain, scientists are also studying the links between DRD2 and other dopamine receptor genes and various psychiatric illnesses and response to anti-psychotic medication. For example, one study has found an (unconfirmed) link between one (different) form of the DRD2 gene and schizophrenia²¹. This study is not yet published and could be wrong, but NicoTest customers should be aware that further research could reveal information that they do not want to know. This has happened in the past with a different genetic test: a gene that had been linked to risk of heart disease was later found to have a link with increased risk of Alzheimer's Disease.

Some studies have linked genetic variations in the 'nicotine metabolism gene' CYP2A6 with risk of cancer, although this link also remains uncertain.

3.2 Lack of medical involvement

Because the test is being sold over the internet (and sales in high street pharmacies are planned), doctors will have no information about the test. They will not be able to check the evidence for the test; ensure it is properly interpreted; or give further information if new studies change the evidence or link one of the genes to a disease. G-Nostics limit all communication to email and could not provide face-to-face information or counselling if necessary.

GeneWatch believes that genetic tests should only be marketed through doctors and should be regulated so that they can be properly interpreted.

3.3 Privacy and genetic discrimination

Anyone taking a genetic test should be aware that there is currently no legislation to prevent insurers or employers asking for genetic test results and using them to decide who gets insurance or a job. There is currently a voluntary agreement between the insurance industry and the Government not to use most genetic test results for most policies, but this agreement ends in 2006. If requests are made for genetic test results after this date they will be made to the person applying for the insurance policy or job (not to g-Nostics Ltd) and failure to reveal them could render an insurance policy invalid.

Conclusions

Better treatment of nicotine addiction is an area where genetic research might prove useful in the future²². This is because a better understanding of nicotine addiction might lead to a better understanding of what helps smokers to quit. It is also possible that genetic tests might help to match smoking cessation treatments to genetic make-up at some point in the future. However, the role of genes in nicotine addiction and treatment

is still poorly understood and the role of other factors (including chance) means that scientists do not yet know if this approach to medicine will work²³. Therefore these genetic tests are currently only useful for research - selling them to members of the public is at best premature. In its rush to market NicoTest™, g-Nostics Ltd is misleading its potential customers.

The NicoTest™ is at best a waste of money. Men in particular have nothing to gain by buying a test which the evidence already shows is not likely to be useful for them. The NicoTest could also mislead smokers and potentially harm health because people are likely to be given wrong advice about how to best increase their chance of quitting smoking.

More information about the need for independent regulation of genetic tests is available on GeneWatch's website^{24,25}.

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