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A cost-effectiveness analysis of genetic testing of the DRD2 Taq1A polymorphism to aid treatment choice for smoking cessation

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Abstract

We conducted a cost-effectiveness analysis of genetic testing for smoking cessation, based on data available from the published pharmacogenetic studies of nicotine replacement therapy and bupropion, and a previous cost-effectiveness analysis of smoking cessation treatments. We use multiparameter evidence synthesis methods to combine evidence on cessation by genotype with evidence on cessation irrespective of genotype (which can be written as a function of genotype-specific parameters). Our intention was to explore the most cost-effective approach to prescribing smoking cessation pharmacotherapy, given the hypothetical availability of a test based on a single-gene variant that has been reported to predict treatment response. We considered four types of treatment: nicotine replacement therapy (NRT) pharmacotherapy, bupropion SR pharmacotherapy, combination NRT and bupropion, and standard care as the control. Two scenarios were investigated, one in which the control represented brief advice and the other in which the control represented individual counseling. Strategies that either do not test for dopamine D2 receptor (*DRD2*) genotype (each individual receives the same treatment), or do test for *DRD2* genotype (treatment allocated according to genotype), were evaluated. Our results indicated that the most cost-effective strategy in our hypothetical example of a single-gene test to aid prescription of smoking cessation pharmacotherapy is to prescribe both NRT and bupropion regardless of genotype, as a first-line treatment for smoking cessation. We conclude that it should not be assumed that genetic tailoring will necessarily be more cost-effective than applying the current “one-size-fits-all” model of pharmacotherapy for smoking cessation. In addition, single-gene tests are unlikely to be cost-effective, partly because the predictive value of these tests is likely to be modest.

Introduction

Nicotine replacement therapies (NRTs), such as nicotine gum, patch, spray, inhaler, and lozenge, and bupropion are currently the principal U.S. Food and Drug Administration (FDA)-approved first-line pharmacological treatments for smoking cessation, although varenicline has recently gained approval (Foulds, 2006). Several meta-analyses have indicated that both NRT (Fiore, Smith, Jorenby, & Baker, 1994; Silagy, Lancaster, Stead, Mant, & Fowler, 2004) and bupropion (Hughes, Stead, & Lancaster, 2004; Scharf & Shiffman, 2004) increase cessation rates compared with placebo. Despite the proven efficacy of these treatments,

however, absolute quit rates remain low, and a number of published studies have reported evidence that genetic variation may be associated with response to smoking cessation pharmacotherapy (Johnstone et al., 2004; Lerman et al., 2002; Lerman et al., 2004; Munafò et al., 2006; Swan et al., 2005; Yudkin et al., 2004). The basic premise of this approach is that inherited differences in drug metabolism and drug targets have important effects on treatment toxicity and efficacy (Evans & Relling, 1999; Poolsup, Li Wan Po, & Knight, 2000). Advantages of a pharmacogenetic approach to the study of smoking cessation treatment include the use of more refined phenotypes for genetic analysis (e.g., prospectively assessed abstinence symptoms, side effects, measures of the rewarding valence of nicotine, and smoking cessation under different treatment conditions) and the use of experimental designs that control the dosing and timing of therapy (Lerman & Niaura, 2002).

The first pharmacogenetic trial of NRT was a placebo-controlled trial of transdermal nicotine patch conducted in a large general practice group in the United Kingdom (Johnstone et al., 2004; Yudkin et al., 2004), which focused on variations in the dopamine pathway, including the dopamine beta hydroxylase (*DBH*) and dopamine D2 receptor (*DRD2*) genes. Nicotine patch was significantly more effective than placebo for carriers of the A1 (T) allele of the *DRD2* gene Taq1A (C32806T) polymorphism, but not those homozygous for the more common A2 (C) allele (Johnstone et al., 2004). The difference in treatment effect between the genotype groups was significant after the first week of treatment but not at the end of treatment. Nicotine patch was found to be highly effective among smokers with both the *DRD2* A1 allele and the *DBH* 1368A allele, and less effective for smokers with other genotypes. This genetic association with treatment response was significant at both 1 week and 12 weeks of treatment, suggesting that the short-term efficacy of nicotine patch may be modulated by *DRD2* and *DBH*. The authors concluded that individual differences in responsiveness to NRT may be partly the result of variations in the dopamine pathway, given the known effects of nicotine on dopamine release and activation of postsynaptic dopamine receptors. These genes are unlikely to serve simply as markers for level of dependence, as there was no observed main effect of genotype on cessation.

Data also exist on the relationship between *DRD2* genotype and response to bupropion pharmacotherapy, although not on *DBH* genotype. In two pharmacogenetic analyses of data from placebo-controlled trials, bupropion was found to be highly effective in individuals homozygous for the *DRD2* A2 allele, compared with carriers of the A1 allele (David et al., 2007; Lerman et al., 2003). A statistically significant moderating effect of *DRD2* genotype on response to bupropion compared with placebo was observed in only one of these studies (David et al., 2007), although in the other study there was a similar qualitative observation of higher abstinence rates among individuals homozygous for the A2 allele using bupropion (Lerman et al., 2003). A pooled analysis of data from these two studies indicated a significant gene $\times$ treatment interaction (data available on request). Evidence from an open-label trial of bupropion pharmacotherapy indicates that women who are homozygous for the A2 allele have improved cessation rates compared with those who have one or more copies of the A1 allele (Swan et al., 2005).

Findings to date exhibit some consistency, with reduced-function alleles of the *DRD2* gene (e.g., Taq1A1) predicting better response to NRT, and increased-function alleles (e.g., Taq1A2) predicting better response to bupropion. This overall picture is complicated, however, by evidence that the widely investigated *DRD2* Taq1A polymorphism alters an amino acid in a previously undescribed protein kinase gene (*ANKK1*) near the *DRD2* locus (Neville, Johnstone, & Walton, 2004). However, this finding does not rule out an association with the *DRD2* gene, since data from the HapMap project revealed that the Taq1A variant is in linkage disequilibrium with other variants in the *DRD2* gene, but not with variants in the *ANKK1* gene (www.hapmap.org).

Although the potential for increasing quit rates by individually tailoring smoking treatment by genotype is promising, research remains in its infancy (Munafò, Shields, Berrettini, Patterson, & Lerman, 2005). In addition to replicating the existing findings regarding the moderating effects of specific genes on treatment outcomes, future studies will need to be designed explicitly to address the question of whether prospective treatment tailoring by genotype enhances smoking cessation rates (Munafò, Shields et al., 2005). It has also been argued that, in parallel to the pharmacogenetics research effort, investigation of the psychosocial, ethical, and health policy issues raised in the translation of research to clinical practice will be needed; this research effort will be informed by the existing clinical genetics literature that pertains to disease genetics (Munafò, Shields et al., 2005).

Despite the lack of evidence, genetic tests for variants reported to be associated with likelihood of smoking cessation success are commercially available; these tests come with advice regarding the most appropriate pharmacotherapy for an individual. For example, in the United Kingdom, smokers can buy a genetic test package that includes follow-up advice online. The package contains a device to take a pinprick of blood, which the customer places on an absorbent pad and sends to a laboratory for DNA analysis. The results are given in conjunction with a personally tailored plan to stop smoking, including advice on the pharmacological treatment most appropriate to an individual's genetic makeup. Advice about behavioral changes, alternative therapies, and other ways to succeed in stopping smoking also is offered. These tests currently retail for approximately £100 (US\$185), which includes ongoing Internet-based behavioral support.

As more tests become commercially available, and as evidence for the association of specific genetic variants with treatment response accumulates, there is likely to be pressure for such tests to be offered by health care providers. In the United Kingdom, interventions require approval by the National Institute for Health and Clinical Excellence before they can be offered through the National Health Service. This process includes assessing the cost per quality-adjusted life-year (QALY) gained as a result of the intervention. A QALY reflects both the quantity and quality of life: It takes 1 year of perfect-health life expectancy to be worth 1, but regards 1 year of less-than-perfect life expectancy as less than 1. Thus an intervention that results in a patient's living for 4 years rather than dying within 1 year, and in which quality is 0.6 on the continuum, will generate a net QALY gain of 1.8 (i.e., $[4 \times 0.6] - [1 \times 0.6]$).

We conducted a cost-effectiveness analysis of genetic testing for smoking cessation, based on the evidence available on the effect of the *DRD2* gene Taq1A polymorphism on cessation rates for NRT (Johnstone et al., 2004) and bupropion (David et al., 2007; Lerman et al., 2003) and a previous cost-effectiveness analysis of smoking cessation treatments (Woolacott et al., 2002). We intended to explore the most cost-effective approach to prescribing smoking cessation pharmacotherapy given the hypothetical availability of a test based on a single-gene variant that has been reported to predict treatment response and that may offer a simple choice between two treatment options. We used Bayesian multiparameter evidence synthesis methods (Ades & Sutton, 2005), which allowed us to combine evidence on functions of parameters—specifically, evidence on cessation by genotype with evidence on cessation irrespective of genotype (which can be written as a function of genotype-specific parameters; Minelli, Thompson, Tobin, & Abrams, 2004; Salanti, Higgins, & White, 2006). Although we accept that treatment response is certainly polygenic in nature, and that our analysis represents an oversimplification of any likely future genetic tailoring interventions, it is timely to consider the possible cost-effectiveness of such an approach. Furthermore, the methods presented here can be extended to incorporate evidence on multiple genetic tests.

Method

Decision problem

The economic evaluation presented here assessed whether it is cost-effective to screen for the *DRD2* gene Taq1A (C32806T) polymorphism and treat those with the CC (A2A2) variant differently from those with the CT and TT (A2A1 and A1A1) genotypes. In line with previous economic evaluations for smoking cessation (Woolacott et al., 2002), we considered four types of treatment: NRT pharmacotherapy, bupropion SR pharmacotherapy, combined NRT and bupropion, and standard care as the control. As in previous studies (Woolacott et al., 2002), we considered two scenarios, in which the control represented either brief advice or individual counseling. For a given control scenario, there were 10 different strategies (Table 1). Strategies S1-S4 did not test for *DRD2* genotype and each individual received the same treatment. Strategies S5-S10 tested for *DRD2* genotype and allocated treatments according to the resulting genotype (CC vs. CT or TT). Table 2 summarizes all parameters and data sources, which are described in detail below.

Effectiveness model and data sources

We denote the 12-month cessation probabilities by p_{CON} , p_{NRT} , p_{BUP} , and p_{N+B} , for the control, NRT, bupropion, and both NRT and bupropion, respectively. We modeled these probabilities on a log-odds (logit) scale (this ensures values between 0 and 1):

$$\begin{aligned} \text{logit}(p_{NRT}) &= \text{logit}(p_{CON}) + d_{NRT} \\ \text{logit}(p_{BUP}) &= \text{logit}(p_{CON}) + d_{BUP} \\ \text{logit}(p_{N+B}) &= \text{logit}(p_{CON}) + d_{N+B} \end{aligned} \quad (1)$$

Equation (1) says that the log-odds of cessation under each treatment is equal to the log-odds of cessation under the control plus the relevant log-odds ratio of cessation under treatment compared with the control (d_{NRT} , d_{BUP} , and d_{N+B} for NRT, bupropion, and both NRT and bupropion, respectively).

Previous literature reviews (Song et al., 2002; Woolacott et al., 2002) provide summary log-odds ratios $y_{NRT} = \text{logit}(p_{NRT}) - \text{logit}(p_{CON}) = 0.513$, $y_{BUP} = 0.742$, and $y_{N+B} = 0.975$ for the three treatments options, together with standard errors $s_{NRT} = 0.0383$, $s_{BUP} = 0.1337$, and $s_{N+B} = 0.242$. These data inform us about d_{NRT} , d_{BUP} , and d_{N+B} directly, and we model the uncertainties in the log-odds ratios with normal likelihoods:

$$\begin{aligned} y_{NRT} &\sim \text{Normal}(d_{NRT}, s_{NRT}^2) \\ y_{BUP} &\sim \text{Normal}(d_{BUP}, s_{BUP}^2) \\ y_{N+B} &\sim \text{Normal}(d_{N+B}, s_{N+B}^2) \end{aligned} \quad (2)$$

Following Woolacott and colleagues (2002), we considered two scenarios for the control 12-month cessation probability, p_{CON} . We assumed a 1% spontaneous annual quit rate, plus an additional 5.1% using brief advice (3-10 min) as the comparator or an additional 11.2% using more intensive individual counseling (>10 min) as the comparator (Nielsen & Fiore, 2000). Including the uncertainty reported in these effects (Nielsen & Fiore, 2000), our two control scenarios can be described by normal distributions (constrained to lie between 0 and 1): $p_{CON} \sim \text{Normal}(0.051, 0.016^2)$ for the brief advice control and $p_{CON} \sim \text{Normal}(0.112, 0.0135^2)$ for the individual counseling control. As in previous studies (Woolacott et al., 2002), we assumed that the relative effects d_{NRT} , d_{BUP} , and d_{N+B} given by equation (1) were the same for both control scenarios.

To incorporate the results of pharmacogenetic trials on the efficacy of the NRT patch vs. placebo (Johnstone et al., 2004) and of bupropion vs. placebo (David et al., 2007; Lerman et al., 2003) by *DRD2* Taq1A genotype, we need to extend our model to allow for genotype. Let

the 12-month cessation probabilities by treatment and genotype be p_{NRT}^{CC} , $p_{NRT}^{T^*}$, p_{BUP}^{CC} , and $p_{BUP}^{T^*}$ with log-odds ratios d_{NRT}^{CC} , $d_{NRT}^{T^*}$, d_{BUP}^{CC} , and $d_{BUP}^{T^*}$ for CC and $T^*=\{CT \text{ or } TT\}$, respectively. Again, we model cessation probabilities on a log-odds scale:

$$\begin{aligned} \text{logit}(p_{NRT}^{CC}) &= \text{logit}(p_{CON}) + d_{NRT}^{CC} \\ \text{logit}(p_{NRT}^{T^*}) &= \text{logit}(p_{CON}) + d_{NRT}^{T^*} \\ \text{logit}(p_{BUP}^{CC}) &= \text{logit}(p_{CON}) + d_{BUP}^{CC} \\ \text{logit}(p_{BUP}^{T^*}) &= \text{logit}(p_{CON}) + d_{BUP}^{T^*} \end{aligned} \quad (3)$$

Only the relative effect (log-odds ratio) depends on genotype; we assume that the cessation rate on the control does not depend on genotype.

The 12-month cessation data from the pharmacogenetic studies (David et al., 2007; Johnstone et al., 2004; Lerman et al., 2003) are in the form of binomial counts (Table 3), which provide information on log-odds ratios d_{NRT}^{CC} , $d_{NRT}^{T^*}$, d_{BUP}^{CC} , and $d_{BUP}^{T^*}$ through a logistic regression model of the form of equation (3), but with genotype-specific control terms estimated as nuisance parameters specific to each study.

To combine the pharmacogenetic evidence (David et al., 2007; Johnstone et al., 2004; Lerman et al., 2003) with the NRT and bupropion evidence from previous work (equation 2), we need to be able to write the log-odds ratios d_{NRT} and d_{BUP} , as a function of genotype-specific parameters (equation 3). In a population in which a proportion, ϕ , have genotype CC and a proportion, $(1-\phi)$, have $T^*=\{CT \text{ or } TT\}$, the 12-month overall cessation probability is a weighted average of the genotype-specific cessation probabilities:

$$\begin{aligned} p_{NRT} &= \phi p_{NRT}^{CC} + (1-\phi) p_{NRT}^{T^*} \\ p_{BUP} &= \phi p_{BUP}^{CC} + (1-\phi) p_{BUP}^{T^*} \end{aligned} \quad (4)$$

Together, equations (1) and (4) give the overall log-odds ratio in this population as a function of genotype-specific parameters:

$$\begin{aligned} d_{NRT} &= \text{logit}(p_{NRT}) - \text{logit}(p_C) \\ &= \text{logit}(\phi p_{NRT}^{CC} + (1-\phi) p_{NRT}^{T^*}) - \text{logit}(p_C) \end{aligned}$$

Similarly,

$$d_B = \text{logit}(\phi p_{BUP}^{CC} + (1-\phi) p_{BUP}^{T^*}) - \text{logit}(p_C) \quad (5)$$

We assume that the proportion of genotype CC in the studies on which our analysis is based (David et al., 2007; Johnstone et al., 2004; Lerman et al., 2003) are representative of the population of smokers seeking help to quit. In total these studies found 849 out of 1,468 individuals with genotype CC (Table 3). If we assume a beta (a_0, b_0) prior distribution for the proportion of genotype CC, ϕ (where a_0 and b_0 are very close to 0, to give an uninformative prior), then the a posteriori distribution for ϕ is a beta (849,619) distribution, which has mean 0.58 and 95% confidence interval (CI) of 0.55-0.60.

The evidence from previous work (Woolacott et al., 2002) informs d_{N+B} directly (equation 2), and d_{NRT} and d_{BUP} indirectly, which are a function of genotype-specific parameters (equation

5). We therefore can combine the pharmacogenetic data (David et al., 2007; Johnstone et al., 2004; Lerman et al., 2003) with the overall NRT efficacy data (Woolacott et al., 2002) through this common model. The model fit was good, and no evidence of inconsistency between these two sources of data was apparent.

We take a Bayesian approach, and put flat normal priors (centered on 0, with variance 1,000) on all parameters to be estimated (log-odds ratios d_{N+B}^{CC} , d_{BUP}^{T*} , d_{NRT}^{CC} , and d_{NRT}^{T*} and control log-odds for the pharmacogenetic studies).

Economic model and data sources

Incremental benefits—We converted 12-month cessation probabilities, p , to lifetime cessation probabilities:

$$\pi = (1 - \text{relapse}) p, \quad (6)$$

where *relapse* is the relapse rate given 12-month cessation, to obtain π_{CON} , π_{NRT} , π_{BUP} , π_{N+B}^{CC} , π_{BUP}^{T*} , π_{NRT}^{CC} , and π_{NRT}^{T*} .

Woolacott and colleagues (2002) reported an average relapse rate of 40% (range=30%-50%). If we assume a beta (a_0, b_0) prior distribution for the relapse rate, *relapse* (where a_0 and b_0 are very close to 0, to give an uninformative prior), then the a posteriori distribution for *relapse* is a beta (38,57) distribution, which has mean 0.4 (95% CI 0.3-0.5). More recent results have shown lower relapse rates of 30% (95% CI 23.5%-37.5%; Etter & Stapleton, 2006), which can be represented by a beta (48,112) distribution. We present results for *relapse* ~ beta (48,112) in a sensitivity analysis.

The quality-adjusted life-years saved (*QALY*) per lifetime cessation is also based on the Woolacott study (Woolacott et al., 2002), which reported an average value of 2.7 (range=1.35-4.05). This can be represented by the normal distribution $QALY \sim N(2.7, 0.474)$ constrained to be non-negative.

For strategies S1-S4, in which there is no test, incremental benefit is the additional probability of lifetime cessation converted to QALYs, and translated to monetary units by multiplying by willingness to pay per QALY, λ (Table 1). For example, strategy S3 is to use bupropion, so the additional probability of lifetime cessation is $(\pi_{BUP} - \pi_{CON})$, and so the incremental benefit of bupropion (S3) over the control (S1) is $(\pi_{BUP} - \pi_{CON}) * QALY * \lambda$.

For strategies S5-S10, in which we do test for genotype, incremental benefit is a weighted sum of the incremental benefit for the two genotypes, where the weights represent the proportion of each genotype in the population, ϕ (Table 1). For example, strategy S10 is to use bupropion

for genotype CC, with an additional probability of lifetime cessation of $(\pi_{BUP}^{CC} - \pi_{CON})$, and NRT for genotype T* with an additional probability of lifetime cessation of $(\pi_{NRT}^{T*} - \pi_{CON})$.

The weighted average additional probability of cessation is with an additional probability of lifetime cessation of $\phi (\pi_{BUP}^{CC} - \pi_{CON}) + (1 - \phi) (\pi_{NRT}^{T*} - \pi_{CON})$, and the incremental benefit over the control (S1) is

$$(\phi (\pi_{BUP}^{CC} - \pi_{CON}) + (1 - \phi) (\pi_{NRT}^{T*} - \pi_{CON})) * QALY * \lambda.$$

Incremental costs—All costs are reported in 2001 prices. Woolacott and colleagues (2002) treat the uncertainty in incremental costs, c_{NRT} , c_{BUP} , and c_{N+B} , for NRT, bupropion,

and both NRT and bupropion, compared with the control via a sensitivity analysis for the cheapest, average, and most-expensive scenarios. However, we found that our results were not sensitive to these scenarios and therefore report results for the average-cost scenario only. The incremental costs also depend on the control scenario, brief advice or individual counseling (see Table 2 for assumed values).

We assume the test costs £10 and requires additional consultation time, which, following Woolacott and colleagues (2002), we take to cost £13.80 for a specific consultation for smoking-cessation advice, making a total cost of $c_{TEST} = £23.80$. We would expect this cost to be higher if gold-standard good laboratory practice methods are used, and so also present results for a total cost of $c_{TEST} = £33.80$. Test kits are available commercially for £100, so we also present results for $c_{TEST} = £100$ as an absolute upper bound for National Health Service costs.

For strategies S1-S4, where there is no test, the incremental costs are simply the incremental costs of the treatments (Table 1). For strategies S5-S10, the incremental cost is the cost of the test, c_{TEST} , plus a weighted sum of incremental cost for each genotype, where the weights represent the proportion of each genotype in the population, ϕ (Table 1). For example, strategy S10 is to use bupropion for genotype CC, with an incremental cost of c_{BUP} , and NRT for genotype T* with an incremental cost of c_{NRT} . The weighted average incremental cost is then $\phi c_{BUP} + (1-\phi)c_{NRT}$.

Cost-effectiveness analysis

The cost-effectiveness analysis is based on incremental net benefit (INB), which is simply the difference between incremental benefit and incremental cost. We present the results as cost-effectiveness acceptability curves, which show the probability that each strategy is the most cost-effective (i.e., has the highest INB) plotted against willingness to pay per QALY, £ λ .

Implementation

We used a Bayesian Markov Chain Monte Carlo (MCMC) simulation framework, implemented in WinBUGS 1.4.1 (www.mrc-bsu.cam.ac.uk/bugs/), to synthesize the evidence, allowing us to simultaneously estimate the efficacy parameters and propagate the uncertainty into the cost-effectiveness analysis (Cooper, Sutton, Abrams, Turner, & Wailoo, 2004). The WinBUGS code can be found at www.bris.ac.uk/cobm/research/mpes.

Results

Regardless of the control scenario and the cost of the test, strategy S4 (offer both NRT and bupropion to all) has the highest probability of being cost-effective, followed by S10 (test and offer bupropion if CC and NRT if TT or CT), then S3 (offer bupropion regardless of genotype). These results are presented Figure 1. Table 4 shows, for the intensive counseling control scenario, the lifetime and 12-month cessation rates by treatment and genotype. The benefits of NRT were greatest for those with the CT or TT variant and the benefits of bupropion greatest for the CC variant, driving the effectiveness of strategy S10. However, the combined NRT and bupropion therapy (S4) provided the greatest mean effectiveness, although substantial uncertainty surrounds this estimate.

For example, at a willingness to pay per QALY of £30,000 and using individual counseling as the control, expected incremental net benefit, E(INB), is £7,130 for S4 compared with £4,945 for S10 and £4,256 for S3 (Table 5). In this case, the probability that S4 is most cost-effective is 0.76, compared with 0.19 for S10 and only 0.03 for S3.

An alternative approach to the cost-effectiveness analysis is to report incremental cost effectiveness ratios (ICERs). The ICERs for strategies that are not dominated are 0.027 for S4

relative to S3, and 0.015 for S3 relative to S1, at a willingness to pay per QALY of £30,000. However, it is preferable to work with INBs than ICERs to fully represent the uncertainty in incremental costs and benefits described by probabilistic models (Briggs, Scupher, & Claxton, 2006).

Whereas E(INB) is greater for the individual counseling control scenario, decreases with the cost of the test, and increases with decreasing relapse rates, the results for the probability of being cost-effective are robust to changes in these modeling assumptions (Table 5, Figure 1). Our results therefore suggest that testing for genotypes of the *DRD2* gene is unlikely to be cost-effective from a National Health Service perspective.

Discussion

Our results indicate that the most cost-effective strategy in our hypothetical example of the availability of a single-gene test to aid prescription of smoking cessation pharmacotherapy is to prescribe both NRT and bupropion as a first-line treatment for smoking cessation, with testing and prescribing bupropion if CC and NRT if T+ as the next most cost-effective strategy. Our example is, of course, somewhat unrealistic, in that it assumes a single-gene test to aid prescription. Nevertheless, it demonstrates that the cost-effectiveness of genetic tailoring of treatment cannot necessarily be assumed.

The public perception of bupropion is more negative in the United Kingdom than it is in other countries where it is licensed for use as a smoking cessation aid, such as the United States, because of a number of high-profile adverse events following its being licensed in the United Kingdom in 2001. Although these adverse events may have been related partly to a relative lack of familiarity among U.K. physicians (where it is not licensed as an antidepressant, unlike in the United States), this means that the most cost-effective strategy indicated by our analysis may not be workable in primary care. Indeed, recommending bupropion on the basis of the results of a genetic test may encourage patients who would otherwise be reluctant to use this pharmacotherapy to do so. This possibility will require independent testing, possibly using analogue methods (Wright, Weinman, & Marteau, 2003).

However, we have adopted a relatively conservative cost estimate of £10 for the hypothetical genetic test in our analysis. As mentioned previously, the commercial tests currently available cost substantially more than this. Although these tests likely look for a (small) number of gene polymorphisms, rather than a single polymorphism as in our hypothetical case, this is offset by the fact that the effect size estimate we used was derived from the first published studies of genetic associations with NRT and bupropion response, and is therefore likely to be an overestimate of any true effect size (Trikalinos, Ntzani, Contopoulos-Ioannidis, & Ioannidis, 2004).

Few studies provide data that would enable the question of the likely cost-effectiveness of genetic testing to be addressed, partly because existing studies are not directly comparable in terms of either the genetic variants investigated or the treatment arms employed (or both), and partly because no prospective studies exist that explicitly test whether genetic testing and consequent tailoring of pharmacotherapy improves the likelihood of smoking cessation success. Moreover, treatment response to smoking cessation pharmacotherapy is likely to be under the influence of a large number of genes, each of small effect. To date, few studies have investigated more than one variant simultaneously, and none has studied more than two or three, largely because the very large sample sizes needed to simultaneously test multiple gene effects and gene×gene interactions are not available.

Various assumptions made in our analysis should be borne in mind when considering the results of this analysis. We have followed previous work (Woolacott et al., 2002) closely, and our

analysis relies on the validity of this health technology assessment. This seems a reasonable approach, since this work represents the main economic evaluation of pharmacotherapy for smoking cessation to date. In fact, the multiparameter evidence synthesis approach (Ades & Sutton, 2005) has allowed us to combine all the available evidence, incorporating the evidence on overall efficacy irrespective of genotype (Woolacott et al., 2002) with all the relevant pharmacogenetic data.

We have also assumed that the relative effects of treatment are the same regardless of the control scenario. However, a more intensive counseling control scenario may attenuate treatment effects. Further, we have assumed that the probability of cessation under each control scenario does not depend on genotype. How realistic this assumption will be depends on the pathways through which the genetic factors operate to influence cessation. If genotype affects only an individual's ability to metabolize the active treatment agent, then this seems a reasonable assumption. However, if genotype acts on some other pathway relating to a propensity to respond to counseling, for example, then we would anticipate that the probability of cessation under control conditions would depend on genotype.

In the absence of any other information, we have assumed that the proportion of individuals with genotype CC found in three pharmacogenetic studies (David et al., 2007; Johnstone et al., 2004; Lerman et al., 2003) are representative of the proportion of genotype CC in the United Kingdom population of European ancestry seeking help to stop smoking. This assumption would certainly seem justified if genetic information was collected concurrently alongside the original trial. However, in the NRT study (Johnstone et al., 2004), these data were collected some time later, after a median interval of 8 years and obtaining a response rate of 767 out of the original 1,612 subjects. It is possible that response rate for the blood samples was not independent of genotype; for instance, response rate may depend on cessation success, which may depend on genotype. Indeed, in the NRT study, evidence indicated that included participants were older than nonparticipants, more likely to be female, better attenders in the original trial, and more successful quitters, although at the start of the trial they showed the same level of nicotine dependence (Johnstone et al., 2004). However, the genetic data from the bupropion studies was collected at trial entry, precluding the possibility of selection biases operating. The fact that $p(CC)$ in all three studies is very similar supports our assumption. It is worth noting, however, that all three studies explicitly excluded participants of non-European ancestry, in order to avoid potential effects of population stratification related to differences in baseline genotype frequencies between groups of differing ancestry. Therefore, the results of these studies, and, by extension, the results of the present study, cannot be generalized beyond populations of European ancestry.

Uncertainty also exists around the various treatment and test costs. We found that the results obtained were not sensitive to the different cost scenarios investigated in the previous economic evaluation (Woolacott et al., 2002).

Finally, our model is somewhat unrealistic in that it considers cessation rates for a single intervention but defines QALYs in terms of lifetime cessation. The majority of smokers willing to attempt to stop smoking once are likely to be willing to do so again if they fail at the first attempt (indeed, for the majority of smokers, this is the route via which long-term abstinence is achieved). Therefore, the incremental benefit is likely to be an overestimate, although this should not affect the relative incremental benefit. Also, offering treatment advice on the basis of a genetic test to an individual who subsequently fails to stop smoking may result in reduced motivation to make further attempts (Munafò, Lerman, Niaura, Shields, & Swan, 2005; Munafò, Shields et al., 2005). Although no data currently exist to test this possibility directly, analogue studies suggest genetic feedback may decrease the perceived value of will-power in a cessation attempt (Wright et al., 2003).

Based on current information, the optimal strategy (highest INB) is to offer both NRT and bupropion to all smokers seeking help to stop smoking. However, uncertainty exists as to whether this is the correct decision, with a probability of around 0.76 that this is the most cost-effective strategy. This raises the question as to whether there is value in collecting further evidence to reduce the uncertainty around this decision and, in particular, whether we should consider testing and offering bupropion to those of genotype CC, and NRT otherwise (Strategy S10), which has a probability of around 0.19 of being the most cost-effective strategy. An expected value of information analysis can address this question (Raiffa & Schlaiffer, 1967). The expected value of perfect information (EVPI) measures the value in learning about the model parameters perfectly (i.e., from an infinitely sized trial). For illustration, at a willingness to pay per QALY of £30,000, using the individual counseling control scenario (cost of test=£23.80), we obtain an EVPI of £932 million, suggesting that there may well be value in carrying out further research. This assumes an average of 4 million smokers wishing to quit per year in the United Kingdom (National Institute for Clinical Excellence, 2002), and a 10-year lifetime of the intervention, discounted at 3.5% per annum. In practice, of course, we can never eliminate uncertainty altogether, so that EVPI is an upper limit on the value of further research. Also, this assumes that we collect further information on all of the model parameters where uncertainty exists, not just the efficacy parameters. To investigate this further would require a detailed expected value of information analysis, which is beyond the scope of this paper.

Our results represent the application of cost-effectiveness analytical techniques to a hypothetical scenario based on a case study of a single report, and these results may therefore not reflect the true cost-effectiveness of future genetic tests for tailoring of smoking cessation pharmacotherapy based on multiple-gene variants. Nevertheless, two main conclusions can be drawn. First, it should not be assumed that genetic tailoring will necessarily be more cost-effective than applying the current “one-size-fits-all” model of pharmacotherapy for smoking cessation. Second, single-gene tests (or, very likely, gene tests that test for only a handful of variants) are unlikely to be cost-effective, partly because the predictive value of these tests is likely to be modest. This is particularly the case given that the genetic effect size on which we based our calculations is likely to be an overestimate of the true effect size. As more pharmacogenetic data, and more comparable studies, become available, it will be possible to implement the methods used here to develop increasingly sophisticated cost-benefit analyses of the potential value of genetic testing for tailoring of smoking cessation pharmacotherapy.

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Figure 1. Cost-effectiveness acceptability curves for (a) brief advice control (cost of test=£23.80), (b) individual counseling control (cost of test=£23.80), and (c) individual counseling control (cost of test=£100). BUP, bupropion; NRT, nicotine replacement therapy.

Table 1
Strategies under consideration in the cost-effectiveness analysis of a genetic test to tailor smoking cessation treatment

Strategy	Test	Treatment for CC genotype	Treatment for CT or TT genotypes	Incremental benefit (£)	Incremental cost (£)
S1	No	CON	CON	0	0
S2	No	NRT	NRT	$(\pi_{NRT} - \pi_{CON}) * Q_{ALY} * \lambda$	c_{NRT}
S3	No	BUP	BUP	$(\pi_{BUP} - \pi_{CON}) * Q_{ALY} * \lambda$	c_{BUP}
S4	No	NRT+BUP	NRT+BUP	$(\pi_{N+B} - \pi_{CON}) * Q_{ALY} * \lambda$	c_{N+B}
S5	Yes	CON	NRT	$(1 - \phi) (\pi_{NRT}^{T*} - \pi_{CON}) * Q_{ALY} * \lambda$	$c_{TEST} + (1 - \phi) c_{NRT}$
S6	Yes	CON	BUP	$(1 - \phi) (\pi_{BUP}^{T*} - \pi_{CON}) * Q_{ALY} * \lambda$	$c_{TEST} + (1 - \phi) c_{BUP}$
S7	Yes	NRT	CON	$\phi (\pi_{NRT}^{CC} - \pi_{CON}) * Q_{ALY} * \lambda$	$c_{TEST} + \phi c_{NRT}$
S8	Yes	NRT	BUP	$(\phi (\pi_{NRT}^{CC} - \pi_{CON}) + (1 - \phi) (\pi_{BUP}^{T*} - \pi_{CON})) * Q_{ALY} * \lambda$	$c_{TEST} + \phi c_{NRT} + (1 - \phi) c_{BUP}$
S9	Yes	BUP	CON	$\phi (\pi_{BUP}^{CC} - \pi_{CON}) * Q_{ALY} * \lambda$	$c_{TEST} + \phi c_{BUP}$
S10	Yes	BUP	NRT	$(\phi (\pi_{BUP}^{CC} - \pi_{CON}) + (1 - \phi) (\pi_{NRT}^{T*} - \pi_{CON})) * Q_{ALY} * \lambda$	$c_{TEST} + \phi c_{BUP} + (1 - \phi) c_{NRT}$

Note. BUP, bupropion; CON, control; NRT, nicotine replacement therapy. Incremental benefit and incremental cost are summarized for each strategy (see Method section of the main text for definitions of parameters).

Summary of model parameters and data sources

Table 2

Parameter	Description	Assumed values	Data sources
p_{CON}	12-month cessation probability in control (CON) arm	Brief advice: $p_{CON} \sim N(.051, .016^2)$ Counseling: $p_{CON} \sim N(.122, .0135^2)$	Nielson & Fiore (2000)
$d_{NRT}^{CC}, d_{NRT}^{I*}, d_{NRT}^{CC}, d_{NRT}^{I*}, d_{BUP}^{CC}, d_{BUP}^{I*}, p_{NRT}^{CC}, p_{NRT}^{I*}, p_{BUP}^{CC}, p_{BUP}^{I*}$	Genotype- and treatment-specific log-odds of cessation under nicotine replacement therapy (NRT) Genotype-specific log-odds of cessation under bupropion (BUP)	Functions of $d_{NRT}^{CC}, d_{NRT}^{I*}, d_{NRT}^{CC}, d_{NRT}^{I*}, d_{BUP}^{CC}, d_{BUP}^{I*}$ and d_{N+B} (see equations 1 and 3) $\phi \sim Beta(849, 619)$	Johnstone et al. (2004) Lerman et al. (2003), David et al. (2007)
ϕ	Genotype- and treatment-specific 12-month cessation probabilities		
p_{BUP}, p_{N+B}	Proportion of CC genotype		
p_{NRT}, p_{BUP}	12-month cessation probabilities over all genotypes	Functions of $\phi, p_{NRT}^{CC}, p_{NRT}^{I*}, p_{BUP}^{CC}, p_{BUP}^{I*}$ (see equation 4) Functions of $p_{CON}, p_{NRT}, p_{BUP}$ (see equation 5) Functions of $p_{NRT}^{CC}, p_{NRT}^{I*}, p_{BUP}^{CC}, p_{BUP}^{I*}$ $p_{NRT}, p_{BUP}, p_{N+B}$ (see equation 6)	Johnstone et al. (2004), Lerman et al. (2003), David et al. (2007)
$d_{NRT}, d_{BUP}, d_{N+B}$	Log-odds ratios over all genotypes		
$\pi_{NRT}^{CC}, \pi_{NRT}^{I*}, \pi_{NRT}^{CC}, \pi_{NRT}^{I*}, \pi_{BUP}^{CC}, \pi_{BUP}^{I*}, \pi_{CON}^{CC}, \pi_{CON}^{I*}, \pi_{NRT}, \pi_{BUP}$	Lifetime cessation probabilities		Woolacott et al. (2002)
π_{N+B}			
$relapse$	Relapse rate given 12-month cessation	$relapse \sim Beta(38, 57)$	Woolacott et al. (2002)
$QALY$	Quality-adjusted life-years saved per lifetime cessation	$QALY \sim Normal(2.7, .689^2)$	Woolacott et al. (2002)
c_{TEST}	Cost of genetic test	$c_{TEST} = £23.80$	
$c_{NRT}, c_{BUP}, c_{N+B}$	Incremental costs for NRT, BUP, and both NRT and BUP	Brief advice: $c_{NRT} = £71.97, c_{BUP} = £72.55, c_{N+B} = £144.52$ Counseling: $c_{NRT} = £67.83, c_{BUP} = £64.28, c_{N+B} = £132.11$	Woolacott et al. (2002)
c_{CON}	Cost for control strategy	Brief advice: $c_{CON} = £3.53$ Counseling: $c_{CON} = £35.25$	Woolacott et al. (2002)

Table 3

Abstinence data (12-month) by *DRD2* genotype for nicotine replacement therapy (NRT) versus placebo and bupropion (BUP) versus placebo

		12-Month abstinence		
Genotype	Treatment	Yes	No	Total
Johnstone et al. (2004)				
CC	NRT patch	25	191	216
	Placebo	20	206	226
CT or TT	NRT patch	23	137	160
	Placebo	14	136	150
David et al. (2007)				
CC	BUP	14	59	73
	Placebo	12	77	89
CT or TT	BUP	11	52	63
	Placebo	12	54	66
Lerman et al. (2003)				
CC	BUP	19	110	129
	Placebo	10	106	116
CT or TT	BUP	12	89	101
	Placebo	7	72	79

Table 4
Posterior means (95% credible intervals) for lifetime and 12-month cessation probabilities by treatment and genotype

	Control	NRT	BUP	NRT+BUP
Lifetime cessation				
CC		.11 (.06-.16)	.14 (.09-.21)	
CT or TT		.12 (.07-.19)	.10 (.05-.17)	
Combined	.07 (.05-.09)	.11 (.08-.14)	.13 (.09-.17)	.16 (.10-.24)
12-Month cessation				
CC		.18 (.11-.25)	.24 (.16-.33)	
CT or TT		.21 (.12-.30)	.17 (.09-.28)	
Combined	.12 (.10-.15)	.19 (.15-.23)	.21 (.16-.27)	.27 (.18-.38)

Note. BUP, bupropion; NRT, nicotine replacement therapy. The table is incomplete because (a) we assume cessation rate on the control is independent of genotype; and (b) it is not possible, from the available data, to estimate cessation by genotype on the combined NRT+BUP strategy. Control, individual counseling.

Table 5
Posterior mean incremental net benefit and probability of being cost-effective

	S4: NRT+BUP	S10: BUP if CC; NRT if TT or CT	S3: BUP
CON: Brief advice only; $c_{TEST} = £23.50$			
E(INB)	£4,112	£2,732	£2,360
p(CE)	0.765	0.185	0.036
CON: Individual counseling;			
E(INB)	£7,130	£4,945	£4,256
p(CE)	0.763	0.191	0.034
CON: Individual counseling;			
E(INB)	£7,130	£4,935	£4,256
p(CE)	0.764	0.189	0.035
CON: Individual counseling;			
E(INB)	£7,130	£4,868	£4,256
p(CE)	0.772	0.180	0.38
CON: Individual counseling; $relapse \sim Beta(48,112)$			
E(INB)	£8,331	£5,777	£4,948
p(CE)	0.762	0.193	0.035

Note. BUP, bupropion; NRT, nicotine replacement therapy. Posterior mean incremental net benefit, E(INB), and the probability of being cost-effective (greatest INB), p(CE), for five modelling scenarios and for the three top strategies, S4, S10, and S3, when willingness to pay per QALY is £30,000.