Personalized Smoking Cessation: Interactions between Nicotine Dose, Dependence and Quit-Success Genotype Score

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Improving and targeting nicotine replacement therapy (NRT) are cost-effective strategies for reducing adverse health consequences for smokers. Treatment studies document the efficacy of precessation NRT and support important roles for level of nicotine dependence and precessation smoking reduction in successful quitting. However, prior work has not identified the optimal precessation dose or means for personalizing NRT. Genome-wide association has identified groups of genomic markers associated with successful quitting, allowing us to develop a v1.0 "quit-success" genotype score. We now report influences of v1.0 quit-success genotype score, level of dependence and precessation smoking reduction in a smoking cessation trial that examined effects of 21 versus 42 mg/24 h precessation NRT. Four hundred seventy-nine smokers were randomized to 21 or 42 mg NRT, initiated 2 wks prior to target quit dates. We monitored self-reported abstinence and end–expired air carbon monoxide (CO). Genotyping used Affymetrix arrays (Santa Clara, CA, USA). The primary outcome was 10-wk continuous smoking abstinence. NRT dose, level of nicotine dependence and genotype scores displayed significant interactive effects on successful quitting. Successful abstinence also was predicted by CO reductions during precessation NRT. These results document ways in which smoking cessation strategies can be personalized based on levels of nicotine dependence, genotype scores and CO monitoring. These assessments, taken together, can help match most smokers with optimal NRT doses and help rapidly identify some who may be better treated using other methods.

INTRODUCTION

Cigarette smoking is a significant cause of premature death and disease (1). Successfully quitting and maintaining abstinence reduce these risks to smokers (2–4). However, success rates following attempts to quit smoking remain modest. One year after unaided attempts to quit smoking, abstinence rates are less than 5% (5,6). Even with pharmacologic aids that include nicotine replacement therapy (NRT), bupropion and varenicline, long-term abstinence rates are less than 25% (7,8).

Precessation NRT initiates nicotine patch treatment 2 wks prior to a target quit date (9,10). The 21 mg/24 hour precessation dose used to date is well tolerated by most smokers (9,10) and consistently enhances quit rates: recent meta analyses show a 1.8–2.2–fold greater likelihood of success than conventional NRT (11,12). However, neither dose/response data nor clear cut recommendations for personalizing precessation NRT have been reported.

More effective smoking cessation might result from personalizing existing treatments based on characteristics of individual smokers. Previous research has identified phenotypic and genotypic variables that might aid in predicting likelihood of success in smoking cessation and/or differential responses to different treatment regimens. In smoking cessation trials, smokers who score higher on the Fagerström Test for Nicotine Dependence (FTND), and thus display more prominent physiological dependence on nicotine, experience lower rates of success from conventional NRT regimens and may derive greater benefits from higher NRT doses (13–15). In a trial of precessation NRT with conventional, 21 mg/24 hour dosing, smokers with higher FTND scores displayed less benefit than those with lower scores (10). We thus hypothesized, *a priori*, that more highly dependent smokers and smokers who find it more difficult to quit with conventional NRT doses might require

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higher NRT doses, both before and after their target quit dates.

Aside from the level of nicotine dependence, other features could help to personalize NRT. After initiation of precessation NRT, individual differences in abilities to decrease end–expired air carbon monoxide (CO) concentrations provide measures of reduced *ad lib* smoking that strongly predict the ability to achieve abstinence (10). Inherited predispositions also are likely to play large roles. Classical genetic studies strongly support the idea that individual differences in abilities to achieve abstinence have significant genetic determinants (16). Genome-wide association and candidate gene molecular genetic studies of quit success have identified a number of candidate "quit-success" alleles (17,18). No individual variant provides a large effect, raising several of the issues discussed in recent reviews (19–22). Nevertheless, GWA data sets from multiple independent smoking cessation samples identify many of the same small chromosomal regions to extents that, overall, are virtually never found by chance (18). In accordance with these recent findings, we have both a) formulated and used a version 1.0 genetic score as an initial, testable index of genetic risk for quit success and b) anticipated (and sought in primary analyses), interactions between this score and level of nicotine dependence.

We thus now report a comparison of 21 and 42 mg/day precessation NRT in smokers categorized based on levels of nicotine dependence, v1.0 quit-success genotype scores and changes in expired air CO during the 2-week precessation treatment period. We document the previously reported predictive value of CO reductions during precessation treatment. We also identify novel interactive effects of genotype score, dependence level and nicotine dose in influencing smoking abstinence outcomes in both European American and African-American smokers. We describe suggestions for personalized precessation NRT that arise from this work, especially as it is replicated in additional samples.
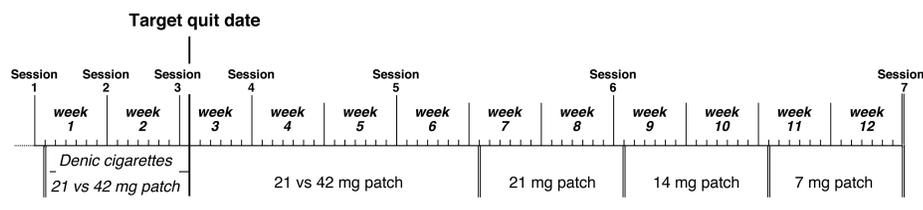

Figure 1. Study timeline.

MATERIALS AND METHODS

Study Design

The study had a randomized, double-blind, parallel-arm, placebo-controlled factorial design with two levels of nicotine dependence and two nicotine doses. Cigarette smokers interested in quitting were subdivided *a priori* into low and high dependence subgroups (FTND scores ≤6 or >6, respectively) (23) and were randomly assigned to 21 mg/24 h or 42 mg/24 h nicotine patch doses.

Recruitment, eligibility and compensation. Adult smokers expressing a desire to quit smoking were recruited through newspaper, radio and television advertisements, flyers and word-of-mouth, and were screened by telephone and physical examination at one of four North Carolina centers. Participants provided informed written consent, reported smoking an average of ≥10 cigarettes that each yielded ≥0.5 mg of nicotine, displayed end–expired air CO ≥10 ppm and failed to display any exclusionary feature on history, physical exam or laboratory evaluation (Supplement 1). Participants were compensated up to $140 for seven sessions.

Study Procedures

After screening and enrollment in the study, participants returned to the research center for seven sessions (Figure 1), during which brief (<15 min) supportive counseling was provided, clinical trial materials were dispensed and dependent measures assessed. Dependent measures included self-reported smoking, end–expired air CO, withdrawal symptoms and other adverse effects.

Each participant wore two skin patches daily for 8 wks, beginning 2 wks prior to the target quit data (see Figure 1). In the 21-mg nicotine dose condition, one active patch (Glaxo-SmithKline, Brentford, Middlesex, UK) was applied in the morning and one placebo patch (Rejuvenation Labs, Salt Lake City, UT, USA) applied at noon. In the 42-mg nicotine dose condition, two active patches were worn. NRT doses were gradually reduced beginning 4 or 6 wks after the quit date for the 42 and 21 mg/24 h groups, respectively. Participants with sleep disturbances removed patches at bedtime and applied new ones upon awakening. Subjects experiencing other symptoms of nicotine toxicity reduced doses until symptoms abated, according to the following sequence: reduce morning patch from 21 to 14 to 7 to 0 mg/d then discontinue the afternoon patch. All participants were provided with denicotinized cigarettes (<0.05 mg nicotine yield; Vector Tobacco Co., Mebane, NC, USA) to smoke during the 2-wk precessation period, to minimize the likelihood of potential adverse effects of high dose NRT.

Genotyping and assignment of genetic background groups. DNA was extracted from blood, quantitated and genotyped using Affymetrix 6.0 microarrays as described (Supplement S2; (24–27). Genotypes for each individual passed Affymetrix quality control metrics and provided calls for ≥97% of SNP genotypes. Imputation using PLINK (28) with confidence threshold >0.95 determined most missing genotype calls.

Genetic background was assigned for each individual based on principal component analyses of data from all SNPs. Two principal components separated a cluster of individuals, almost all of whom reported European ancestry from

a cluster whose members reported predominantly African ancestry (Supplementary Figure S1). Three individuals who fell between these clusters and identified themselves as being of mixed ethnic/racial backgrounds were classed as indeterminant and excluded from further statistical analyses.

Assignment of v1.0 quit-success genotype scores. Genotypes and v1.0 scores were assigned for each participant by investigators blinded to clinical phenotype. We assessed alleles at the 12,058 SNPs (29; Appendix A) (see http://www.sciencedirect.com/science/Miami MultiMediaURL/B6T63-4W8KHMN-2/ B6T63-4W8KHMN-2-1/5019/html/ S0376871609000921/85fe35dc441ab55778 3c8a1ce3038044/f.doc?MMCv = widget), for which at least 1 of 3 previously reported smoking cessation success clinical trial samples identified nominally highly significant ($P < 0.01$) differences between successful versus unsuccessful quitters, weighting data from these SNPs based on strength and replicability of the associations (Supplement 3; 18).

Analyses

The primary outcome was continuous abstinence from the target quit date through the end of treatment (10 wks) was assessed based on self-reports of continuous abstinence (that is, no lapses) that were confirmed by end–expired CO levels ≤10 ppm. Participants who withdrew from the study or were lost to follow-up were classified as nonabstinent. Secondary abstinence outcomes included (a) 4-wk continuous abstinence during wks 7–10 after the target quit date, and (b) 7 d, point abstinence at 6 months.

Logistic regression analyses were conducted to seek statistically significant effects on quit success based on: nicotine patch dose (21 mg versus 42 mg), level of dependence (≤6 versus >6 FTND score), and v1.0 quit-success genotype scores (≤ median versus > median), with emphasis on interactions among these factors. In preplanned analyses, we compared individuals with upper to lower half v1.0 quit-success scores, seeking: (a)

to avoid any assumptions regarding the linearity of influences across the range of genotype scores; (b) to ensure that equal numbers of subjects were classified "low" or "high" in each racial/ethnic subgroup; and (c) to parallel the analyses used for FTND scores and changes in CO levels (see below). Median v1.0 scores and proportions of smokers with FTND scores ≤6 were similar in European American (384; 54%) and African-American (392; 49%) participants.

To verify that participants assigned to each of the four treatment groups did not exhibit disparate v1.0 quit-success genotype scores due to stochastic influences (30), we conducted one preplanned interim analysis of data from the first 203 participants. There was no evidence for significant stratification in individuals assigned to each of the four treatment arms (data not shown). In addition, quit-success v1.0 genotype scores appeared to interact with dependence level and nicotine dose. Highly dependent smokers with low quit-success genotype scores benefited to greater extents from the 42-mg NRT dose (data not shown).

On the basis of the results of interim analyses and our *a priori* hypotheses positing interactions between dose and level of dependence, the final analysis of the complete data set (n = 457) included the following terms: nicotine dose (21 mg versus 42 mg); FTND dependence score

(≤6 versus >6); quit-success genotype score (≤ median versus > median); nicotine dose × dependence; and nicotine dose × dependence × genotype score. Separate follow-up analyses for the European American and African-American samples explored the robustness of the nicotine dose × dependence × v1.0 genotype score interaction.

Frequencies with which adverse events occurred in the two nicotine dose conditions were compared using χ^2 tests.

*All supplementary materials are available online at www.molmed.org.*

RESULTS

Most smokers who contacted the research center met eligibility criteria and were enrolled. Most enrollees participated successfully (Table 1, Figure 2).

Logistic regression of data from the primary outcome, 10-wk continuous abstinence, yielded a significant three-way interaction between nicotine dose, dependence and quit-success genotype score ($P = 0.015$), exponentiated coefficient = 0.56 (95% CI = 0.35–0.91). The interaction noted in interim analysis of the initial set of subjects also was noted in separate analysis of data from the second half of the subject group (data not shown). In the entire group of subjects, the two-way interaction of nicotine dose and FTND score also was significant ($P = 0.02$), exponentiated coefficient = 1.78

Table 1. Baseline participant characteristics.

	Low dependence smokers		High dependence smokers	
	21 mg	42 mg	21 mg	42 mg
Age, mean (SD)	43.2 (11.1)	42.2 (11.4)	45.0 (11.2)	43.8 (10.9)
Gender (male/female)	45/70	46/70	51/67	60/58
Race/ethnicity				
European American, n (%)	92 (80.0)	80 (70.0)	99 (83.9)	87 (73.7)
African-American, n (%)	19 (16.5)	27 (23.3)	17 (14.4)	24 (20.3)
Other, n (%)	4 (3.5)	9 (7.8)	2 (1.7)	7 (5.9)
Nicotine yield, mean (SD)	0.87 (0.2)	0.90 (.90)	0.91 (.28)	0.96 (.27)
Cigarettes/day, mean (SD)	19.4 (8.0)	18.9 (6.6)	29.4 (9.9)	28.2 (11.2)
Years smoked, mean (SD)	23.8 (10.5)	22.7 (11.1)	26.8 (11.6)	25.6 (10.6)
FTND score, mean (SD)	4.6 (1.6)	4.7 (1.5)	8.0 (1.0)	8.0 (1.0)
End–expired air CO, mean (SD)	24.9 (9.5)	24.3 (9.7)	31.0 (13.1)	29.7 (10.8)
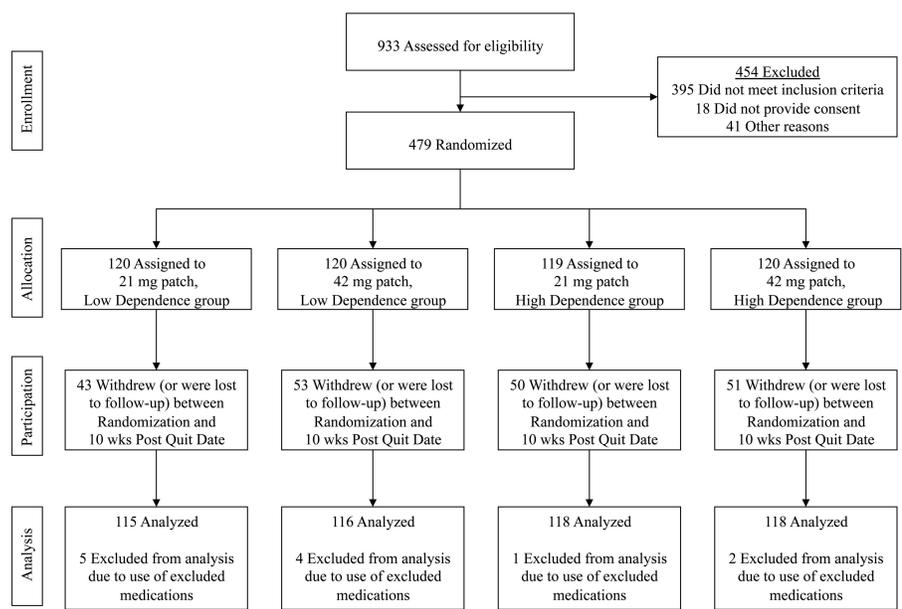
Figure 2. Depiction of participant recruitment, eligibility assessment, allocation to treatment conditions and disposition.

(95% CI = 1.10–2.87). Figure 3 displays the rate of 10-wk continuous abstinence as a function of nicotine dose, dependence level and genotype score. The 42-mg nicotine dose condition tended to enhance treatment outcome for highly dependent smokers with low v1.0 scores (*P* = 0.06). By contrast, this high-dose patch impeded abstinence for less dependent smokers with low v1.0 scores (*P* = 0.009). The nicotine dose × dependence × genotype score interaction also was significant for 4-wk continuous abstinence at the end of treatment (*P* = 0.02, exponentiated coefficient = 0.62, 95% CI = 0.42–0.93), a secondary outcome (Supplementary Figure S2). Moreover, the 6-month-point abstinence results showed
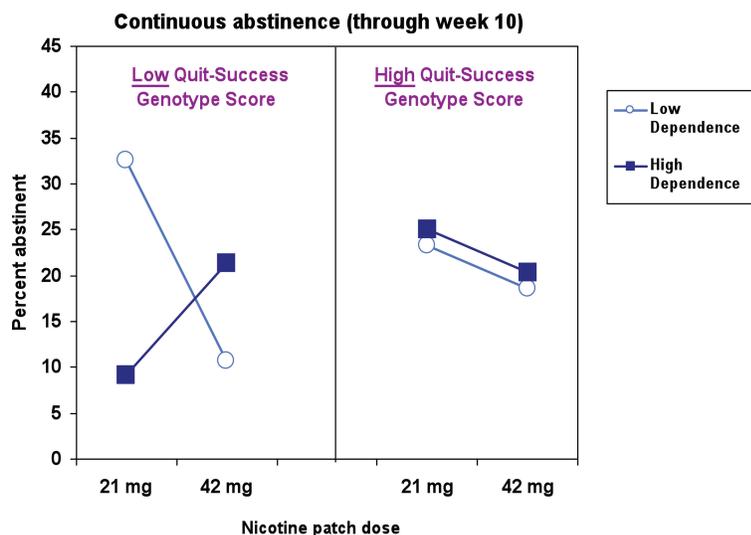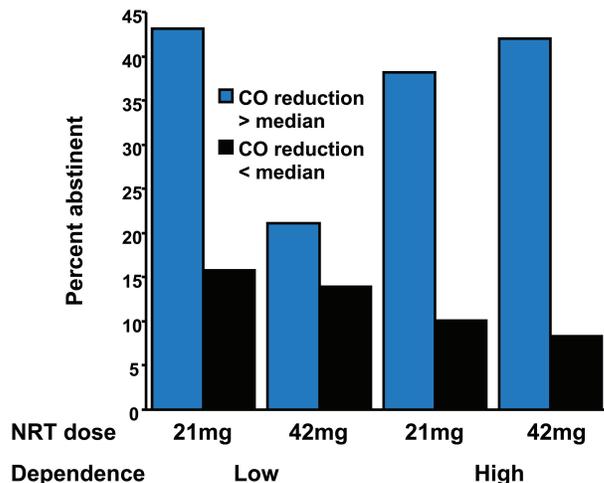
the same pattern of three-way interaction (*P* = 0.03, exponentiated coefficient = 0.62, 95% CI = 0.40–0.96); see Supplementary Figure S2.

There were concordant results from analyses that separated European American and African-American smokers. For smokers with European ancestry (*n* = 369), the 10-wk continuous abstinence outcome showed a nicotine dose × dependence × v1.0 genotype score interaction (*P* = 0.05, exponentiated coefficient = 0.60, 95% CI = 0.35–1.00). With respect to 4-wk continuous abstinence and 6-month-point abstinence, the subsample showed a similar, though nonsignificant, trend (*P* = 0.12, exponentiated coefficient = 0.71, 95% CI = 0.46–1.09; *P* = 0.19, exponentiated coefficient = 0.72, 95% CI = 0.45–1.17). For smokers with African ancestry (*n* = 88), this three-way interaction displayed a trend similar to that noted for the entire sample for both 10-wk (*P* = 0.15, exponentiated coefficient = 0.33, 95% CI = 0.07–1.48) and 4-wk continuous abstinence (*P* = 0.08, exponentiated coefficient = 0.38, 95% CI = 0.13–1.12). The three-way interaction did reach significance in this subsample for 6-month-point abstinence (*P* = 0.02, exponentiated coefficient = 0.20, 95% CI = 0.05–0.78).

Abstinence outcomes also were predicted by individuals' abilities to reduce smoking during the 2-wk precessation period, as measured by decreases in end–expired air CO levels. Smokers whose CO dropped by more than the median (55.6% decrease) showed a substantially higher rate of 10-wk continuous abstinence than smokers who did not show this decrease: 37.6 % versus 11.2% (*P* < 0.001, odds ratio = 4.77, 95% CI = 2.81–8.11; for results from each treatment group, see Figure 4). A similar result was obtained for 4-wk continuous abstinence (52.1% versus 26.5%; *P* < 0.001, odds ratio = 3.01, 95% CI = 1.97–4.60) and 6-month-point abstinence (40.2% versus 18.9%; *P* < 0.001, odds ratio = 2.89, 95% CI = 1.83-4.57).

However, the precessation decrease in CO did not explain all of the influ-

Figure 3. Smoking abstinence as a function of nicotine patch dose, dependence and quit-success genotype score.

Figure 4. Continuous 10-wk smoking abstinence as a function of end–expired air CO reduction during the 2-wk precessation period.

This "baseline" characteristic of each participant was joined by data from CO reductions during precessation NRT, since prior data supported the predictive power of such CO reductions.

Remarkably, each of these participant characteristics exerted a significant direct or interactive influence on smoking cessation success in ways that depended on NRT dose. Our results support the hypothesis that different nicotine doses are more efficacious for different subgroups of smokers. The higher, 42 mg/24 h NRT dose benefited the highly dependent smokers with low v1.0 genotype scores. By contrast, this high dose impeded quitting by less-dependent smokers with low v1.0 scores. The robust interactions between nicotine dose, dependence and genotype score are supported by: 1) the results of interim analysis having been borne out in the entire sample; and 2) replication within separate subsamples of smokers with European or African ancestry. This use of data from sets of SNPs that individually provide modest association signals appears to document clinical utility for genome-wide association data from this trait with polygenic genetic architecture (19–22).

In addition to supporting a personalized treatment approach that takes into account baseline smoker characteristics, our results suggest that treatment algorithms could adapt therapeutic approaches based on smokers' initial reduction in *ad lib* smoking in response to precessation nicotine patch treatment. Smokers whose end–expired air CO level decreased >55.6% before the target quit date exhibited abstinence rates more than three times higher than those showing smaller decreases in CO. By rapidly identifying individuals who show insufficient CO reductions during precessation NRT and hence are less likely to quit, we might avoid failed quit attempts through prompt application of alternative and/or more intensive treatments. Several such treatments, bupropion and varenicline, are more costly than NRT and appear to display greater risks (33–35). A logical, stepped care ap-

ences on quit success provided by other measures of individual differences. The three-way interaction of nicotine dose, FTND score and quit-success genotype score remained statistically significant, even after inclusion of a term in the logistic regression model that reflected CO decreases ($P = 0.04$ for 10-wk abstinence).

Adverse Effects

Treatment was generally well tolerated. Three percent of participants withdrew from the study because of adverse effects. The most frequently reported patch-related adverse effects were: vivid dreams (83.5%), itching or burning (55.3%), insomnia (47.2%), rash (20.7%), nausea (15.9%), headache (26.1%), and vomiting (2.5%). There was a trend toward more frequent nausea in the 42-mg dose condition ($P = 0.06$). Each of two women who received 42-mg doses reported syncope on one occasion, each in conjunction with nausea or vomiting; neither reported any sequelae.

DISCUSSION

Nicotine replacement strategies, including precessation NRT, aid smoking cessation with low cost and well-characterized safety profile. Personalizing NRT in ways that are informed by precessa-

tion CO reductions and interactions between dependence and a v1.0 "quit-success" genotype score appears to offer an attractive way of increasing cessation success for many smokers.

The plausibility of the results of this study is increased by several *a priori* considerations. The extent of nicotine dependence, assessed by FTND score, was likely, *a priori*, to influence success in quitting smoking, based on much evidence from many studies of smoking cessation, including some with precessation NRT (5,9). Genetic influences on smoking cessation were also likely, *a priori*, to influence smoking cessation success, based on the substantial heritable influences documented in twin studies (16). Retrospective molecular genetic studies identified SNP markers that provided nominally significant associations with quit success in 1 or more of 3 initially reported samples (18). Many of the genomic regions identified by these SNPs also have been identified by studies of quit success in three additional samples (31,32). Since none of these associations is of large magnitude, we assembled a v1.0 molecular genetic measure relevant to quit success by combining data from groups of SNPs that provide nominally significant associations with this phenotype in three prior studies.

proach would thus entail initial use of precessation NRT, assignment of nicotine dose based on dependence level and quit-success genotype scores, identification of individuals who do not reduce CO sufficiently and prompt reassignment of such individuals to alternative therapies. Identification of the best alternatives for individuals who display insufficient CO reductions in response to NRT appears to provide a fruitful area for future study.

The current study, while offering support for the interactive effects of NRT dose, dependence level and quit-success genotype score, also has limitations. This randomized clinical trial might not replicate in other samples or generalize to clinical practice. The United States Food and Drug Administration (USFDA) has not approved use of precessation NRT, NRT doses >21 mg/24 hours or denicotinized cigarettes in conjunction with NRT. Initial studies do support efficacy of denicotinized cigarettes (36). Precessation treatment is approved in Australia and the United Kingdom, and is under consideration by other regulatory authorities. The v1.0 genotype score, while displaying substantial promise, was based on data from European American participants in only three sets of clinical trials (18). We anticipate that the power of this approach will be enhanced further as data from additional studies allows us to improve this score. Finally, even after future results replicate those in the present report, it will be necessary to surmount barriers to acceptance prior to implementation in smoking cessation clinical trials and/or in clinical practice. These barriers include costs, perceptions about genotyping by researchers, physicians and patients, and other practical issues such as turnaround time for testing (37,38).

In summary, the present results provide support for a personalized and adaptive approach to smoking cessation treatment, which tailors the dose of NRT to the baseline phenotypic and genotypic characteristics of the individual smoker, and adapts the treatment based on early

assessments of therapeutic response. In the foreseeable future, implementing such an algorithm in clinical practice should markedly enhance smokers' chances of ridding themselves of their health-damaging addiction to cigarettes.

ACKNOWLEDGMENTS

DISCLOSURE

GR Uhl and JE Rose are listed as inventors for a patent application filed by Duke University based on genomic markers that distinguish successful quitters from unsuccessful quitters in data from other clinical trials.

REFERENCES

1. Adhikari B, Kahende J, Malarcher A, Pechacek T, Tong V. (2008) Smoking-attributable mortality, years of potential life lost, and productivity losses – United States, 2000–2004. *MMVR Wkly*. 57:1226–8.
2. Godtfredsen NS, *et al*. (2008) COPD-related morbidity and mortality after smoking cessation: status of the evidence. *Eur. Respir. J*. 32:844–53.
3. Teo KK, *et al*. (2006) Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 368:647–58.
4. White WB. (2007) Smoking-related morbidity and mortality in the cardiovascular setting. *Prev. Cardiol*. 10:1–4.
5. Moore D, *et al*. (2009) Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ*. 338:b1024.
6. Ward KD, Klesges RC, Zbikowski SM, Bliss RE, Garvey AJ. (1997) Gender differences in the outcome of an unaided smoking cessation attempt. *Addict. Behav*. 22:521–33.
7. Gonzales D, *et al*. (2006) Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 296:47–55.
8. Zhu S, Melcer T, Sun J, Rosbrook B, Pierce JP. (2000) Smoking cessation with and without assistance: a population-based analysis. *Am. J. Prev. Med*. 18:305–11.
9. Rose JE, Behm FM, Westman EC, Kukovich P. (2006) Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine Tob. Res*. 8:89–101.
10. Rose JE, Herskovic JE, Behm FM, Westman EC. (2009) Precessation treatment with nicotine skin patch significantly increases abstinence rates relative to conventional treatment. *Nicotine Tob. Res*. 9:1067–75.
11. Shiffman S, Ferguson SG. (2008) Nicotine patch therapy prior to quitting smoking: a meta-analysis. *Addiction*. 103:557–63.
12. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. (2008) Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst. Rev*. 2008 Jan 23(1):CD000146.
13. Johnson EO, Morgan-Lopez AA, Breslau N, Hatsukami DK, Bierut LJ. (2008) Test of measurement invariance of the FTND across demographic groups: assessment, effect size, and prediction of cessation. *Drug Alcohol Depend*. 93:260–70.
14. Jorenby DE, *et al*. (1995) Varying nicotine patch dose and type of smoking cessation counseling. *JAMA*. 274:1347–52.
15. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. (2004) Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst. Rev*. 2002;(4):CD000146.
16. Broms U, Silventoinen K, Madden PA, Heath AC, Kaprio J. (2006) Genetic architecture of smoking behavior: a study of Finnish adult twins. *Twin Res. Hum. Genet*. 9:64–72.
17. Uhl GR, *et al*. (2007) Molecular genetics of nicotine dependence and abstinence: whole genome association using 520,000 SNPs. *BMC Genet*. 8:10.
18. Uhl GR, *et al*. (2008) Molecular genetics of successful smoking cessation: convergent genome-wide association study results. *Arch. Gen. Psychiatry*. 65:683–93.
19. Goldstein DB. (2009) Common genetic variation and human traits. *N. Engl. J. Med*. 360:1696–8.
20. Hirschhorn JN.(2009) Genomewide association studies—illuminating biologic pathways. *N. Engl. J. Med*. 360:1699–701.
21. Hardy J, Singleton A. (2009) Genomewide association studies and human disease. *N. Engl. J. Med*. 360:1759–68.
22. Kraft P, Hunter DJ. (2009) Genetic risk prediction— are we there yet? *N. Engl. J. Med*. 360:1701–3.
23. Fagerström KO, *et al*. (1996) Nicotine dependence versus smoking prevalence: comparisons among countries and categories of smokers. *Tob. Control*. 5:52–6.
24. Johnson C, *et al*. (2006) Pooled association ge-

nome scanning for alcohol dependence using
104,268 SNPs: validation and use to identify alco-
holism vulnerability loci in unrelated individuals
from the collaborative study on the genetics of
alcoholism. *Am. J. Med. Genet. B. Neuropsychiatr.
Genet.* 141:844–53.

25. Liu QR, *et al.* (2006) Addiction molecular genet-
ics: 639,401 SNP whole genome association iden-
tifies many "cell adhesion" genes. *Am. J. Med.
Genet. B. Neuropsychiatr. Genet.* 141B:918–25.

26. Liu QR, *et al.* (2005) Pooled association genome
scanning: validation and use to identify addic-
tion vulnerability loci in two samples. *Proc. Natl.
Acad. Sci. U. S. A.* 102:11864–9.

27. Uhl GR, Liu QR, Walther D, Hess J, Naiman D.
(2001) Polysubstance abuse-vulnerability genes:
genome scans for association, using 1,004 sub-
jects and 1,494 single-nucleotide polymorphisms.
Am. J. Hum. Genet. 69:1290–300.

28. Purcell S, *et al.* (2007) PLINK: a tool set for
whole-genome association and population-based
linkage analyses. *Am. J. Hum. Genet.* 81:559–75.

29. Uhl GR, Drgon T, Li CY, Johnson C, Liu QR.
(2009) Smoking and smoking cessation in disad-
vantaged women: assessing genetic contribu-
tions. *Drug Alcohol Depend.* 104 Suppl 1:S58–63.

30. Uhl GR, Drgon T, Johnson C, Rose JE. (2009)
Nicotine abstinence genotyping: assessing the
impact on smoking cessation clinical trials. *Phar-
macogenomics J.* 9:111–5.

31. Drgon T, *et al.* (2009) Genome-wide association
for nicotine dependence and smoking cessation
success in NIH research volunteers. *Mol. Med.*
15:21–7.

32. Drgon T, *et al.* (2009) Genome-wide association
for smoking cessation success: participants in a
trial with adjunctive denicotinized cigarettes.
Mol. Med. 15:268–74

33. Igarashi A, Takuma H, Fukuda T, Tsutani K.
(2009) Cost-utility analysis of varenicline, an oral
smoking-cessation drug, in Japan. *Pharmacoeco-
nomics.* 27:247–61.

34. Hoogendoorn M, Welsing P, Rutten-van Molken
MP. (2008) Cost-effectiveness of varenicline com-
pared with bupropion, NRT, and nortriptyline
for smoking cessation in the Netherlands. *Curr.
Med. Res. Opin.* 24:51–61.

35. Kuehn BM. (2009) Studies linking smoking-
cessation drug with suicide risk spark concerns.
JAMA. 301:1007–8.

36. Becker KM, Rose JE, Albino AP. (2008) A ran-
domized trial of nicotine replacement therapy in
combination with reduced-nicotine cigarettes for
smoking cessation. *Nicotine Tob. Res.* 10:1139–48.

37. Botkin JR, *et al.* (2010) Outcomes of interest in
evidence-based evaluations of genetic tests.
Genet. Med. 12:228–35.

38. Chung WK. (2007) Implementation of genetics to
personalize medicine. *Gend. Med.* 4:248–65.