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Physician Barriers to Incorporating Pharmacogenetic Treatment Strategies for Nicotine Dependence Into Clinical Practice

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Abstract

Advances in genomics research may improve health outcomes by tailoring treatment according to patients' genetic profiles. The treatment of nicotine dependence, in particular, may soon encompass pharmacogenetic treatment models. Realizing the benefits of such treatment strategies may depend on physicians' preparedness to incorporate genetic testing into clinical practice. This article describes barriers to clinical integration of pharmacogenetic treatments that will need to be addressed to realize the benefits of individualized smoking-cessation treatment.

Smoking, genetics, and nicotine dependence

Smoking continues to be a major global public health problem, accounting for more than 4 million deaths and costing over US$100 billion in health-care costs worldwide annually. Given the plateauing of smoking rates over the past several years, innovative approaches are needed to reignite the decline in smoking rates that were achieved in the latter part of the twentieth century.

Twin, adoption, and meta-analytic studies show that genetic factors account for about two-thirds of individual variability in smoking persistence, cessation attempts, withdrawal symptoms, and duration of cessation.[1] Studies have examined how specific genes affect response to treatments for nicotine dependence, including differential response to nicotine replacement therapies and bupropion as a function of variability in nicotinic pathway genes (*CHRNA4*, *CHRNA5*, *CHRNA2*, *CHRNB2*, *CHAT*), pharmacokinetic candidate genes (*CYP2A6*, *CYP2B6*), dopaminergic pathway genes (*ANKK1*, *DBH*, *DRD2*, *COMT*, *DRD4*, *SLC6A3*), serotonergic pathway genes (*SLC6A4*), and endogenous opioid pathway genes (*OPRM1*).[1] Consistent associations with response to smoking-cessation treatments have been observed for genotypic and phenotypic measures of variation in nicotine metabolism.[1] Using the nicotine metabolite ratio (NMR; ratio of 3′-hydroxy-cotinine to cotinine) as a marker for CYP2A6, smokers characterized as slow metabolizers of nicotine activity show significantly higher rates of smoking cessation using transdermal nicotine or counseling alone than fast nicotine metabolizers.[1] Fast metabolizers of nicotine, when treated with bupropion, show quit rates comparable to slow metabolizers of nicotine.[1] A current trial is evaluating, for the first time, the benefits of the NMR to prospectively tailor the selection of

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CONFLICT OF INTEREST

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smoking-cessation treatments (transdermal nicotine and varenicline; NIH DA020830; http://projectreporter.nih.gov/reporter.cfm). Past retrospective studies, combined with this ongoing prospective trial, offer promise for the potential use of the NMR as one model for individually tailoring treatments for nicotine dependence to increase cessation rates.

Physician barriers to genetic testing for tailoring nicotine dependence treatment

The potential benefits of individualized treatment for nicotine dependence cannot be realized without the willingness of primary care physicians (PCPs) to incorporate genetic assessment into clinical practice. Smokers most often initiate cessation attempts by conferring with their PCPs, yet US studies indicate reluctance among PCPs to adopt genetic testing to individualize smoking-cessation treatment. Despite efforts to increase PCPs' knowledge of clinical genetics, only 4% say they feel prepared to address genetic testing with patients[2]; only ~60% of PCPs have ever ordered a genetic test for any condition, and 74% have ever referred a patient for testing.[2] Furthermore, merely describing a test as "genetic" (vs. non-genetic) reduces physicians' willingness to offer testing by 11% (ref. 3). Approximately one-third of PCPs report reluctance to use genetic testing to tailor smoking-cessation treatment.[3] PCPs in small practices, those with less training in clinical genetics, and those serving large proportions of minority and low-income patients are less likely to have ever provided genetic testing to their patients directly or through referral.[2] PCPs who are current or former smokers themselves, who do not regularly prescribe smoking-cessation treatments to their patients, and who have less positive attitudes about the potential of genetics to improve smoking treatment are less likely to offer testing to tailor smoking-cessation treatment.[3]

Several barriers to genetic testing for nicotine dependence treatment among US PCPs have been identified.[3] First, PCPs have concerns about interpreting and communicating complex test results. Most genetic tests for nicotine dependence involve probabilities, versus a certainty that an outcome will manifest if the mutation is present. In the case of nicotine dependence, psychological and social variables interact with genes to determine smoking-cessation outcomes. Physicians may have difficulty presenting genetic test results that convey probabilities and are influenced by environmental factors. This issue is compounded by the limited training that physicians receive in clinical genetics and physicians' perceptions that they lack the qualifications to interpret and convey genetic information to patients.[4]

Second, PCPs are concerned about the potential for discrimination against patients on the basis of genetic test results because many genes linked to nicotine dependence are also associated with a greater risk for other addictions and psychiatric conditions.[5] Physicians may be reluctant to use genetic information to tailor treatments for nicotine dependence for fear that test results will be used to discriminate against their patients in insurance or employment settings.[5]

Third, there are several practical hurdles associated with incorporating testing into routine medical practice.[3] PCPs have concerns about the burden that genetic testing procedures and feedback protocols will present to their busy practices.[4] Today's PCPs are expected to deliver many services within a short visit, which makes it challenging to address complex behavioral issues such as smoking. Developing the capacity to deliver genetic testing to match smokers to the optimal treatment option in routine clinical practice will be especially difficult for small practices, which make up half of US PCP practices.[4] Additional resources and infrastructure development would be needed to support the application of genetically tailored treatment in small practices. Finally, health-care system differences between

countries, which may influence physicians' ability to incorporate genetic testing procedures for nicotine dependence, should be considered.

Overcoming physician barriers to using genetic information for treating nicotine dependence

Realizing the promise of genomic medicine in health care broadly, and with regard to the treatment of nicotine dependence specifically, depends on addressing barriers PCPs will face in trying to incorporate genetic information into clinical practice. First, systematic efforts are needed to bolster PCPs' education in clinical genetics so that they feel competent to discuss genetic testing with their patients, interpret genetic results, and use test results to guide treatment decisions. Clinical genetics must be more substantially addressed in medical school curricula and training; educational programs on novel pharmacogenetic treatment strategies could be widely and quickly disseminated to PCPs through workshops and Webinars that provide continuing medical education credit. Educational initiatives should include content on bioethics and guidelines for the use of genetic testing, with particular attention to the genetics of psychiatric conditions and addictions.[3] The availability of online clinical decision support through rapidly diffusing health information technology systems may speed physician preparedness. Decision-support systems should be developed such that they can accommodate complex criteria for genetic assessment and implications for treatment decisions for various clinical conditions.

Second, further efforts are needed to prevent the risk that genetic information will be misinterpreted or misused and to educate providers and patients about protections that currently exist. Although the passage of the US Genetic Information Nondiscrimination Act has allayed some fears regarding genetic discrimination, ambivalence about genetic testing —particularly in the context of sensitive phenotypes—persists among patients and clinicians. Additionally, legislative protections are not in place in all countries to ensure that all health-care systems protect individuals from potential adverse effects of genetic testing.

Third, innovative approaches to integrating genetic testing and feedback procedures into clinical care are needed, given physician time constraints and clinical demands. Reimbursement for genetic services is a necessary but not sufficient condition to ensure successful clinical integration. Research is needed to identify the most cost-effective and efficient methods for incorporating genetic testing to tailor individual treatment into medical practice, address barriers articulated by PCPs, and increase the likelihood of physician adoption of efficacious treatment strategies for nicotine dependence.

Conclusions

Genomic medicine holds great promise for improving treatment efficacy and reducing adverse drug responses. This promise may be particularly salient for treating nicotine dependence, which remains a major international public health problem. Since a PCP is most often a smoker's initial contact regarding quitting, physician preparedness to use genetic testing procedures to guide treatment selection will be critical to realizing the clinical benefit of improved treatment matching. Unfortunately, many physicians report reluctance to use genetic testing for treating nicotine dependence and report barriers to utilizing such technologies to help their patients quit smoking, including the complexity of genetic information, their lack of experience with genetic testing, the possibility of misinterpretation and misuse of genetic test results, and lack of time and resources to integrate genetic testing and feedback procedures into their practice. Consequently, educational changes are needed to better prepare physicians to use genetic testing technologies in their practice; further legal protections and policies are needed to strengthen

patient privacy and confidentiality; novel strategies are needed to address physicians' lack of time and resources; and efforts are needed to ensure that genetic testing and feedback procedures are reimbursed by third-party payers.

Efforts to address these barriers should take into account differences in healthcare systems across different countries. Realizing the promise of pharmacogenetics research on nicotine dependence to improve treatment outcomes will depend largely on our success in reducing the barriers that PCPs will face in using genetic testing to guide treatment decisions for their patients in routine clinical practice.

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References

1. Ray, R.; Schnoll, RA.; Lerman, C. Nicotine dependence and pharmacogenetics. In: Steptoe, A., editor. Handbook of Behavioral Medicine. New York: Springer; 2010.
2. Shields, AE.; Blumenthal, D.; Weiss, KB.; Comstock, CB.; Currivan, D.; Lerman, C. J. Gen. Intern. Med. Vol. 20. 2005. Barriers to translating emerging genetic research on smoking into clinical practice: perspectives of primary care physicians; p. 131-138.
3. Shields AE, Levy DE, Blumenthal D, Currivan D, McGinn-Shapiro M, Weiss KB, et al. Primary care physicians' willingness to offer a new genetic test to tailor smoking treatment, according to test characteristics. Nicotine Tob. Res. 2008; 10:1037–1045. [PubMed: 18584467]
4. Shields AE, Lerman C. Anticipating clinical integration of pharmacogenetic treatment strategies for addiction: are primary care physicians ready? Clin. Pharmacol. Ther. 2008; 83:635–639. [PubMed: 18323859]
5. Levy DE, Youatt EJ, Shields AE. Primary care physicians' concerns about offering a genetic test to tailor smoking cessation treatment. Genet. Med. 2007; 9:842–849. [PubMed: 18091434]