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Preparing the Way: Exploiting Genomic Medicine to Stop Smoking

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Abstract

Clinical medicine of the future is poised to use an individual's genomic data to predict disease risk and guide clinical care. The treatment of cigarette smoking and tobacco use disorder represents a prime area for genomics implementation. The genes *CHRNA5* and *CYP2A6* are strong genomic contributors that alter the risk of heaviness of smoking, tobacco use disorder, and smoking-related diseases in humans. These biomarkers have proven analytic and clinical validity, and evidence for their clinical utility continues to grow. We propose that these biomarkers harbor the potential of enabling the identification of elevated disease risk in smokers, personalizing smoking cessation treatments, and motivating behavioral changes. We must prepare for the integration of genomic applications into clinical care of patients who smoke.

Keywords

smoking; addiction; smoking cessation; genomic medicine; genetics

Implementing Genomic Medicine – the Next Frontier

The large-scale implementation of genomic knowledge into healthcare represents the next frontier in clinical medicine. Recent efforts funded by the National Institutes of Health (e.g., the Implementing Genomics in Practice Program, https://www.genome.gov/27554264/implementing-genomics-in-practice-ignite/), the Centers for Disease Control and Prevention (e.g., the Public Health Genomics Knowledge Base, https://phgkb.cdc.gov/PHGKB/phgHome.action?action=home), as well as private companies such as 23andMe (https://www.23andme.com) are shaping the research, practice, and policy landscapes for large-scale, affordable genomics implementation. Though the majority of work to date has focused on using genomic information to identify risk of cancer and congenital diseases, next phases

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are expanding to a wider range of diseases and disorders, including aspects of behavioral medicine. In addition, an increasing focus on **pharmacogenomics** (see Glossary), where individual responses to specific drug treatments are tied to genomic variation, is the next frontier to personalized treatment.

The treatment of cigarette smoking and tobacco use disorder represents a prime area for genomics implementation. **Genomic variation** characterizes a growing class of biological markers or "**biomarkers**" that objectively measure characteristics that identify biologic processes, pathologic outcomes, or pharmacologic responses. Genomic variation biomarkers underlie the **precision medicine** efforts to personalize approaches to disease prevention and treatment. We are on the cusp of implementing genomic testing into clinical care related to smoking behaviors given our knowledge of variation that predicts heaviness of cigarette smoking **measured by cigarettes smoked per day**, tobacco use disorder, smoking-related disease outcomes, and potentially, pharmacogenomic responses to smoking cessation medications.

Combustible cigarette smoking remains one of the foremost causes of preventable death in both industrialized and developing countries. In the United States, over 36 million people smoke cigarettes [1] and worldwide over one billion use tobacco products (http://www.who.int/gho/tobacco/use/en/). Every year, over 480,000 people die in the U.S. from tobacco-related illnesses [2], and over 6 million people perish worldwide (http://www.who.int/mediacentre/factsheets/fs339/en/). Preventive strategies that regulate tobacco sales and tax tobacco products have significantly decreased smoking initiation over the past 50 years [3]. Yet, in the U.S., 36 million people continue to smoke and 68% report wanting to quit, but only 7% of smokers successfully stop smoking each year [4]. The high addictiveness of nicotine and the ongoing large burden of smoking-related health effects motivate efforts to improve smoking cessation using novel approaches.

Self-reported cigarettes smoked per day is a commonly used and easily collected measure of combustible cigarette consumption [5]. Clinicians and researchers use self-reported cigarettes per day integrated over a lifetime history of smoking to estimate health risks for many cancers, chronic obstructive pulmonary disease, and other smoking-related diseases [6]. In addition to disease risk, smoking more cigarettes per day is correlated with greater dependence on nicotine, resulting in more difficulty with smoking cessation [7]. However, the number of cigarettes smoked does not fully capture the behavior of cigarette smoking; for instance, for the same number of cigarettes smoked, differences in the number of puffs inhaled per cigarette as well as the depth of inhalation can be profound [8, 9]. It is common knowledge that for the same number of cigarettes smoked per day, some individuals are able to quit smoking and others struggle to quit. In addition, the effectiveness of our smoking cessation treatments is modest at best and ineffective for most people who smoke. Heritability estimates indicate that genomic variation drives many of these differences in smoking behaviors and smoking cessation between smokers [10–13]. This backdrop highlights the importance of developing new genomic biomarker tools to better predict outcomes related to combustible cigarette smoking and to promote smoking cessation. In this article, we discuss evidence of genomic variation contributing to smoking behaviors and

propose the gaps that need to be filled to implement genomically-informed smoking cessation.

Genomic Contributors to Smoking Behaviors

We focus on two strong genomic contributors that alter the risk of heaviness of smoking and tobacco use disorder – variation in the genes encoding **nicotinic acetylcholine receptor subunits** and **nicotine metabolism enzymes**. We select these two genomic targets because of their robust connection with smoking heaviness, lung cancer, and chronic obstructive pulmonary disease in well-powered **genome-wide association studies** (GWAS), in addition to their biological plausibility, as described below. GWAS has unequivocally demonstrated that variation in neuronal nicotinic acetylcholine receptor subunit α5 ***(CHRNA5)***, the gene encoding the α5 nicotinic acetylcholine receptor (AChR) subunit, predicts smoking heaviness, later age of smoking cessation, lung cancer, chronic obstructive pulmonary disease, and early mortality (Table 1, Key Table) [13–24]. Similarly, variation in cytochrome P450 2A6 ***(CYP2A6)***, the gene encoding the primary enzyme that metabolizes nicotine, also predicts heavier cigarette consumption, failed smoking cessation, and smoking-related illnesses, **including hypertension and lung cancer** (Table 1) [11, 25–33]. These advances in our knowledge of genomic biomarkers associated with cigarette smoking related morbidity and mortality lay the foundation for genomic implementation to reduce smoking.

The first large-scale genome-wide analysis of tobacco use disorder was conducted in 2007 and identified the *CHRNA5* **single nucleotide polymorphism** (SNP), rs16969968, as being associated with an increasing risk for heaviness of smoking and tobacco use disorder [14, 15]. The association between this variant and smoking-related phenotypes was subsequently confirmed at a genome-wide significance level by multiple independent groups [16, 20, 34]. Research consortia performed a genome-wide association **meta-analysis** that included over 73,000 subjects, and rs16969968 exhibited a highly significant association with cigarettes smoked per day (p value=5.57×10^{-72}) [22]. Although the majority of this genomic research has been conducted with populations of European ancestry, additional studies have demonstrated that *CHRNA5* variation is associated with risk for heavy smoking in European, African and Asian populations [35–37]. Across world populations, variation in *CHRNA5* is associated with altered susceptibility to tobacco use disorder.

Experimental studies have shown how this genomic variation functionally alters biologic responses. The α5 nicotinic acetylcholine receptor subunit combines with other nicotinic subunits to form a pentameric receptor that binds nicotine [38]. The rs16969968 variant causes an amino acid change from aspartic acid to asparagine in the α5 nicotinic receptor subunit [39]. This amino acid change alters receptor function *in vitro*; functional studies indicate reduced receptor response to nicotinic agonists in cells expressing the rs16969968 asparagine coding variant versus the aspartic acid coding variant [40, 41].

In parallel to this work, genomic variation in *CYP2A6*, the gene that encodes the primary enzyme cytochrome P450 2A6 (CYP2A6) that metabolizes nicotine, plays a role in heaviness of smoking and smoking-related illnesses [25, 29, 42, 43]. Nicotine, the key addictive compound in tobacco, is metabolically inactivated by the hepatic enzyme,

CYP2A6 to form **cotinine** (COT) and cotinine is further metabolized to **3'-hydroxycotinine** (3HC) exclusively by CYP2A6 [44, 45]. *CYP2A6* is highly polymorphic and these genomic differences in turn lead to a large variation in rates of nicotine metabolism (from essentially inactive to very rapid) [27, 46, 47]. This inter-individual variation in rates of metabolism of nicotine can contribute to differential addictive risk associated with nicotine intake [48]. Genetically fast metabolizers of nicotine are more likely to smoke more cigarettes per day, be dependent on nicotine, fail smoking cessation, and have a higher risk for smoking-related illnesses such as lung cancer [29, 43, 49–51].

This gene has complex genomic architecture with duplications and deletions, which challenges current genomic testing. Another measure of nicotine metabolism, the ratio of 3'-hydroxycotinine to cotinine, referred to as the **nicotine metabolite ratio** (NMR), has been developed as a validated indicator of genomic variation in *CYP2A6*, representing enzymatic activity in daily smokers (Key table, Table 1) [47, 52, 53]; it is also highly correlated to total nicotine clearance [47]. This measure was created in part to overcome the difficulty in testing genomic variation in *CYP2A6* due to numerous structural variants and high homology with adjacent genes *CYP2A7* and *CYP2A13* [47]. In addition, the NMR captures both genomic variation in *CYP2A6* as well as environmental factors such as other medication use (for example estrogen-containing hormonal therapy) that might influence nicotine metabolism [46]. Thus, genetic variation in both *CYP2A6* and *CHRNA5* create biologically plausible sources of variation in smoking behaviors; CYP2A6 may alter the levels of nicotine for any given dose, and variation in the nicotinic receptor may alter the impact of the nicotine dose on downstream effects.

Smoking Cessation

One of the strongest predictors of failed smoking cessation is the level of dependence on nicotine [7, 54–56]. Genomic variation in *CHRNA5* and *CYP2A6* are among the strongest risk factors for heaviness of smoking and tobacco use disorder, and in turn, both of these genes are related to failed smoking cessation [11, 13, 51, 57]. Variation in *CHRNA5* predicts a later age of smoking cessation at a population-based level, as well as failed smoking cessation during pregnancy [13, 57]. Similarly, variation in *CYP2A6* is associated with differential success rates in smoking cessation [11, 51].

Growing evidence indicates that *CHRNA5* variation is associated with responses to pharmacological treatment and success of pharmacotherapy for smoking cessation [10, 58–61]. Pharmacogenomics is the use of genomic variation to predict the likelihood that a patient will successfully respond to pharmacological treatments. In the case of smoking cessation, there are three Food and Drug Administration (FDA)-approved medications: **nicotine replacement therapy, varenicline**, and **bupropion**. Some studies report a genotype-by-treatment interaction, whereby those with high-risk genomic variants of *CHRNA5* are more predisposed to having difficulty quitting without treatment, and this genetic risk can be ameliorated by pharmacological treatment [10, 12]. However, other studies find no evidence of an association of variation in *CHRNA5* with smoking cessation, nor of a genotype-by-treatment interaction [62, 63]. A Cochrane review of 18 smoking cessation trials investigated whether abstinence rates varied by genetically informed

biomarkers (including *CHRNA5*) within pharmacotherapy treatment arms compared to placebo. The authors tentatively concluded that there may be a gene by treatment interaction for rs16969968, although there is notable heterogeneity between studies [64].

Further studies have examined the role that nicotine metabolism plays in smoking cessation. In general, smokers who are slower metabolizers identified by NMR, present greater quit rates in clinical trials in the placebo arm (consistent with increased spontaneous quitting seen in some studies), and under treatment with the nicotine patch [65, 66]. Faster metabolizers exhibit better treatment responses on varenicline than with the nicotine patch (compared to slow metabolizers), with a more favorable side effect profile [67]. To date, only one prospectively genomically-informed randomized clinical trial has been performed; randomization by NMR (and oversampling slow metabolizers) indicated that faster metabolizers exhibited better quit rates on varenicline versus patch, relative to slow metabolizers; slow metabolizers also presented a worsened side-effect profile for varenicline than faster metabolizers [67]. A key issue in the experimental design for these pharmacogenomics studies is the placebo or behavioral counseling treatment arm, as both genes have an influence on the cessation rate in the absence of pharmacotherapy, which can alter the interpretation of the intervention arm [51]. Further well-designed pharmacogenomics studies comprise a ripe area for investigation moving forward, including conducting adequately-powered, prospective clinical, pharmacogenetic smoking cessation trials. With high quality, valid biomarkers, we may accelerate progress in personalizing treatment for smoking cessation.

Process for Introducing Genomic Evidence to Address Smoking

For genomic applications to enter clinical medicine, key questions should be answered to evaluate components of analytic validity, clinical validity, and clinical utility of a test.

Analytic Validity

Genomic testing for low frequency (0.5% – 5%) and common (>5%) variants yields highly reproducible results, indicating strong analytic validity; indeed, variation in *CHRNA5* can be measured accurately and reliably [68]. Direct genomic testing remains troublesome for variation in *CYP2A6* due to hybrid and copy number variants and high homology to *CYP2A7*, a pseudo gene, although newer methods, including next-generation sequencing, and SNPs identified from GWAS of the NMR, appear to be alleviating this problem [69–72]. Thus, both these genomic regions qualify for analytic validity, if these methods are conducted properly.

The NMR, which captures *CYP2A6*'s enzymatic function, has been extensively tested, demonstrating accuracy and reliability [53, 73]. The relatively long half-life of COT and of 3HC enhance stability over time for COT and 3HC, as well as the resulting NMR, in daily smokers; this stability is evident in both heavy and light cigarette smokers and over different sampling time of day (reviewed in [53]). There is minimal variation in NMR over a 7-day period for daily smokers, and it remains stable over a 44-week range in regular daily smokers and in smokers who are reducing their smoking levels with the help of nicotine

replacement therapy (NRT). Moreover, the NMR is robust to different analytical approaches [53].

Clinical Validity

High-risk genomic variation in these two regions contributes to disease risk across populations, and multiple phenotypic/genotypic relationships have been established as genetic variation in *CHRNA5* and *CYP2A6* has been associated with increased risk of heavy smoking, increased intensity of smoking, as well as smoking-related disease, and mortality [16, 20, 22, 24, 28, 29, 74]. Examples of the additive effect of these two genes together on heaviness of smoking, dependence and lung cancer are described in further detail in [11] and [29].

Evidence for efficacy testing to improve smoking cessation is less strong, as most has relied on retrospective analyses of trials not adequately powered for pharmacogenomic assessment. As previously mentioned, one prospective controlled trial tested smoking cessation pharmacotherapy response based on nicotine metabolism and showed differential responses to pharmacologic treatment between varenicline and nicotine patch based on nicotine metabolism rate; faster metabolizers presented better outcomes on varenicline than the patch, relative to slower metabolizers who presented greater side effects on varenicline [67]. This work will need to be replicated and extended to different ethnicities and types of smokers (including, for example, populations of light smokers, pregnant smokers, e-cigarette users, and individuals with comorbid psychiatric disorders). Nonetheless, the overall body of knowledge about disease risk suggests that pending further validation, testing of both of these genomic regions may have clinical validity.

Clinical Utility

The existing evidence for clinical utility is sparser. The gold standard of clinical utility is the evaluation of results from prospective trials that randomize participants to genomic testing or no genomic testing to compare genomically-informed treatments with usual care [75]. Genetic risk scores are stable over a lifetime, but one significant limitation for the use of NMR is the requirement of recent smoking (cotinine levels need to be in steady-state). Pragmatic trials, which undertake a practical approach to test genomically-informed interventions for smoking cessation integrated into routine medical care, might provide the greatest information about clinical utility [76, 77]. The costs, economic benefits, and degree to which the probabilities of smoking-related behaviors and diseases generated from genomic test results are actionable and changeable in clinical and community settings remains unclear. We deem clinical utility for these genomic applications targeted on smoking cessation to be unknown, and future research should focus on robustly addressing questions of clinical utility.

Ethical, Legal, and Social Implications (ELSI)

The primary ethical, legal, and social concerns involve issues regarding stigmatization, discrimination, and confidentiality associated with genomic testing. Insufficient work to date has been undertaken to address these important concerns when conducting individual genomic tests related to smoking behaviors.

Key Applications and Targets of Genomic Information for Smoking

Significant advances in understanding the genomic variation that underlies smoking behavior have been made, including, as discussed, the well-validated association of *CHRNA5* and *CYP2A6* genomic variation with heavy smoking and smoking-related diseases. Ultimately, this considerable body of evidence should be translated into practical genomic applications that can be integrated routinely in clinical and community settings. We envision at least three applications in which the field of behavioral medicine could apply genomics-informed probabilities to address smoking behaviors and smoking-related diseases based on *CHRNA5* and *CYP2A6* genomic variation.

Risk Stratification in Individuals Who Smoke

Though all individuals who smoke are at increased risk for smoking-related diseases, genomic variation in *CHRNA5* and *CYP2A6* alters this risk beyond the measurement of cigarettes smoked per day [78, 79]. **Risk stratification**, a goal of precision medicine, is a key application of genomic information at an individual level to predict elevated risk for lung cancer, chronic obstructive pulmonary disease, and early mortality [24, 80–82]. Incorporating this genomic information in patient care may prioritize care management efforts such as more intensive interventions for smoking cessation as well as disease screening (e.g., lung cancer screening). Delivering personalized genomic health information directly to individuals is important in its own right to empower personal health-related decision making. This effort is well-aligned with patient-centered approaches to care and research initiatives such as All of Us (https://allofus.nih.gov/), the NIH effort to accelerate research and improve health by taking into account individual differences in lifestyle, environment, and genomics. We posit that testing of *CHRNA5* and *CYP2A6* genomic variation to predict heaviness of smoking and augment risk stratification for lung cancer and other smoking-related lung diseases constitutes the strongest supporting evidence and carries the highest readiness for implementation.

Precision Treatment for Smoking Cessation

Using *CHRNA5* and *CYP2A6* results to identify individuals at higher risk of difficulty with smoking cessation and to potentially guide smoking cessation interventions is a promising area for further investigation. The clinical use of genomic results to inform and optimize smoking cessation pharmacotherapy will reflect a key application in the context of precision medicine. Genomic information on *CHRNA5* and *CYP2A6* predicts an increased risk of failed smoking cessation and thus increased need for pharmacotherapy (i.e., nicotine replacement therapy, varenicline, bupropion) as well as counseling [10, 11, 51, 58]. Genomic variation in these two genes may inform the differential selection of smoking cessation pharmacotherapy to yield maximal effectiveness, while limiting excessive adverse events and unnecessary costs. The strongest evidence supporting this rationale relies on findings reporting differing rates of nicotine metabolism that can prospectively predict differential pharmacologic responses [67]. Further research is needed to clarify the potential utility of genomic results on effectiveness as well as determining the possible side effects to smoking cessation medications. Another area of needed research is the development of biomarkers to predict who may relapse back to smoking after quitting.

Motivating Behavior Change

The return of genomic test results for *CHRNA5* and *CYP2A6* variation directly to the consumer, or in coordination with a health care provider, is potentially a motivator for smoking cessation. As a tangible example, personalized genomic profiles that communicate disease risk (e.g., not elevated, elevated, highly elevated) for lung cancer and other lung diseases, based on their smoking histories as well as *CHRNA5* and *CYP2A6* genomic results, could be given to individuals who smoke [83]. The vast majority of individuals report interest in receiving personal genomic risk results for many diseases and recognize the importance of both behavioral and genomic factors that contribute to illness [84, 85]. Studies which have examined the return of genomic information to alter smoking behaviors have not shown increased smoking cessation [86, 87] However, these studies have not tested genomic variation that is directly related to smoking behaviors and pharmacologic response to treatment such as variation in *CHRNA5* and *CYP2A6* [86, 88]. Only one study has returned genomic information about *CHRNA5* variation and smoking risks and this study did find increased cessation among smokers [83]. The future of precision medicine includes the return of genomic information to individuals. Though this specific use of genomic information clearly has the weakest supporting evidence base to change smoking behavior, it nevertheless, deserves further investigation as our knowledge regarding genomic contributions to smoking behaviors and smoking-related diseases grows.

Concluding Remarks

Genomic variation in *CHRNA5* and *CYP2A6* are currently the only genomic targets nearing entry into clinical medicine for smoking, particularly in the tailoring of smoking cessation. Variation in these genes causes differences in smoking behaviors across world populations. Despite diverse genomic backgrounds, the association between *CHRNA5* and *CYP2A6* genomic variation and smoking-related behaviors is seen in populations of European, Asian, and African ancestry [35–37]. These genomic biomarkers have analytic validity – as they can be accurately and reliably measured, as well as clinical validity – as they have been unequivocally associated with heaviness of smoking and risk of smoking-related diseases [13, 16, 18–20, 22, 25, 28, 30, 37, 43, 89]. Evidence of clinical utility continues to grow [64, 67, 83]; these biomarkers can be used to predict smoking cessation difficulty and potential response to smoking cessation pharmacotherapy, and initial evidence suggests that return of these genomic results may motivate smoking cessation [84, 85]. However, the need remains to better define the potential utility of integrating genomic advances to change smoking behavior and reduce cigarette smoking (see Outstanding Questions and box 1). Large-scale research consortia such as GSCAN (https://gscan.sph.umich.edu/), the GWAS & Sequencing Consortium of Alcohol and Nicotine Use, will define many more genomic regions associated with smoking behaviors in the upcoming year [90]. At this point, we argue that we must continue to test these two (and other yet-to-be defined) genes in relation to smoking-related outcomes and increase the state of readiness for the implementation of genomic applications.

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Laura J. Bierut is listed as an inventor on Issued U.S. Patent 8,080,371,"Markers for Addiction" covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction.

R.F. Tyndale has consulted with Apotex and Quinn Emanuel on unrelated issues.

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Glossary

3’-hydroxycotinine (3HC)
a product of CYP2A6 metabolism of the primary nicotine metabolite, cotinine.

Analytic validity
refers to how well a test predicts the presence or absence of a particular gene or genetic change.

Biomarker
a biological measure found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, condition, or disease.

Bupropion
a prescription medication (antidepressant of the aminoketone class) used to treat smoking by reducing the severity of craving and withdrawal symptoms.

CHRNA5
the gene coding the α5 subunit of nicotinic acetylcholine receptor subunit.

Clinical utility
refers to whether a test can provide information about diagnosis, treatment, or prevention of a disease that will be helpful to a consumer.

Clinical validity
refers to how well a genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.

Cotinine
the predominant metabolite of nicotine. Cotinine is used as a biomarker for exposure to nicotine in tobacco smoke.

CYP2A6
the gene for the cytochrome P450 enzyme 2A6 that oxidizes nicotine to its inactive metabolite cotinine, and cotinine to 3'-hydroxycotinine.

Genome-wide association study
an approach that involves rapidly scanning markers across complete sets of DNA/ genomes, to find genomic variations associated with a particular disease.

Genomic variation
differences in the DNA sequence rom one person to the next.

Meta-analysis
quantitative statistical analysis of several separate but similar studies in order to test the pooled data for statistical significance.

Nicotinic acetylcholine receptor
receptor proteins that respond to the neurotransmitter acetylcholine. Nicotinic receptors also respond to drugs, including nicotine. They are found in the central and peripheral nervous system, muscle, and many other tissues.

Nicotine metabolism enzymes
proteins that metabolize nicotine, the P450 enzyme 2A6 being a predominant enzyme.

Nicotine metabolite ratio (NMR)
the ratio of 3'-hydroxycotinine to cotinine, which correlates with nicotine clearance from the body and is used as a biomarker for CYP2A6 activity.

Nicotine replacement therapy
smoking cessation treatment that supplies a controlled amount of nicotine, but excludes other dangerous chemicals found in cigarettes.

Pharmacogenomics
the study of inherited genetic differences in drug metabolic pathways which affect individual responses to drugs, both in terms of therapeutic effects and adverse effects.

Precision medicine
an emerging approach for disease prevention and treatment that takes into account individual variability in genes, environment, and lifestyle for each person.

Risk stratification
a tool to identify and predict which patients are likely to be at high risk and tailoring the management of their care in order to prevent worse outcomes.

Single nucleotide polymorphism
a variation in a single base pair in a DNA sequence.

Varenicline

a prescription medication used to treat smoking. It is a nicotinic receptor partial agonist—it stimulates nicotine receptors more weakly than nicotine itself.

Highlights

- Advances in DNA sequencing technology and efforts such as the Precision Medicine Initiative are paving the way for the implementation of genomics into clinical medicine.
- Variation in *CHRNA5*, the gene encoding the α5 nicotinic acetylcholine receptor subunit, and *CYP2A6*, the gene encoding the primary enzyme that metabolizes nicotine, predict smoking heaviness, delayed smoking cessation, and risk for smoking-related diseases.
- Despite diverse genomic backgrounds, the association between *CHRNA5* and *CYP2A6* genomic variation and smoking-related behaviors is seen in populations of European, Asian, and African descent.
- Evidence is equivocal regarding the use of *CHRNA5* and *CYP2A6* to predict response to pharmacological treatment for smoking cessation. Adequately-powered, prospective clinical and pharmacogenetics trials are thus needed.

Outstanding Questions Box

- Does providing genomic risk results for *CHRNA5* and *CYP2A6* to individuals who smoke cigarettes motivate smoking cessation?
- Will providing genomic risk results for *CHRNA5* and *CYP2A6* motivate the prescription of pharmacotherapy for smoking cessation by health care providers?
- Will providing genomic risk results *CHRNA5* and *CYP2A6* motivate the use of pharmacotherapy for smoking cessation by individuals who smoke?
- Can genomic variation in *CHRNA5* and *CYP2A6* predict responses to smoking cessation pharmacotherapy?
- How do we address issues of stigmatization, discrimination, privacy, and confidentiality associated with genomic testing for smoking behaviors?
- What are the economic and time costs associated with integrating genomic applications for smoking cessation into routine medical care?

Box 1

Clinician's Corner

- Although clinicians use self-reported cigarettes smoked per day integrated over a lifetime history of smoking to estimate health risks for many smoking-related illnesses, number of cigarettes smoked does not fully capture the behavior of cigarette smoking. For the same number of cigarettes smoked, differences in the number of puffs inhaled per cigarette as well as the depth of inhalation can be profound. These differences lead to differential risk for smoking-related diseases such as lung cancer.
- Genomic variation in two genes that are associated with smoking behaviors (*CHRNA5* and *CYP2A6)* alters risk for smoking-related diseases beyond the measurement of cigarettes smoked per day. This genomic information may be used to prioritize care management efforts such as increased efforts at smoking cessation as well as disease screening (e.g., for lung cancer).
- There are three Food and Drug Administration (FDA)-approved medications for smoking cessation: nicotine replacement therapy, varenicline, and bupropion. In the future, it might be possible to use genomic variation in two key genes, *CHRNA5* and *CYP2A6*, to predict which patients will be more successful at stopping smoking with these medications.
- With the advent of direct-to-consumer genotyping services such as 23andMe, individuals have access to their genetic health information. It is only a matter of time before genomic information may become routinely used in clinical care. Physicians need to prepare for this change and consider the best practices for incorporating genomic information into clinical settings and for sharing genetic results with patients.

Key Table Table 1

Diagnostic Biomarkers of Tobacco Use Disorders

Biomarker	Predictive Ability	Risk	Limitations	Refs
CHRNA5	Smoking heaviness Later age of smoking cessation	Predictive of lung cancer, COPD, early morality	rs16969968 low frequency in African and Asian ancestry Linkage disequilibrium structure differs across world populations	[13–24]
CYP2A6	Smoking heaviness Later age of smoking cessation	Predictive of lung cancer, COPD, hypertension	Difficult to genotype because of complex genetic architecture Linkage disequilibrium structure differs across world populations	[11, 25–30, 33]
NMR	Nicotine metabolism Later age of smoking cessation Smoking cessation with specific pharmacologic therapy		Requires recent smoking	[65–67]

NMR: nicotine metabolite ratio; COPD: Chronic obstructive pulmonary disease; Refs: references