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Review

Nicotine addiction through a neurogenomic prism: Ethics, public health, and smoking

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Studies are under way to examine the neurogenetic factors contributing to smoking behaviors. The combined approaches of genomics, molecular biology, neuroscience, and pharmacology are expected to fuel developments in pharmacogenetics, to create new genetic tests, and ultimately to provide the basis for innovative strategies for smoking cessation and prevention. The emergence of a neurogenomic understanding of nicotine addiction is likely to induce fundamental changes in popular, clinical, and public health views of smoking, which could significantly shape existing practices and policies to reduce tobacco use. Still a nascent area of research, nicotine addiction provides an excellent case study through which to anticipate key ethical and policy issues in both behavioral genetics and the neurogenomics of addictive behaviors.

An emerging genomic prism

Since the beginning of the Human Genome Project, genetic and molecular approaches to disease and to the study of normal physiology have become a dominant paradigm for biomedical research. The effects of this paradigm are increasingly felt throughout clinical practice, by generating new categories of disease—and new conceptual understandings of health—based on genetic mutations and molecular explanations (Baird, 1990; Bell, 1998). The primacy of genetic explanations of disease and health has been defined as "geneticization" (Lippman, 1992). Critical analyses of the process of geneticization—in which genetics is compared with a prism, coloring and diffracting our views of health and disease (Boyle, 1992)—have become a cornerstone for studies of the ethical, legal, and social implications of genetic research and technologies (Duster, 1990; Harris & Schaffner, 1992; Murray Jr., 1996; Nelkin & Lindee, 1995; Rapp, 1988; Rothenberg, 1997; Shuster, 1992). The metaphor of light refracted through a prism has proved useful in imagining how our understanding of human disease or behavior will be shaped by the assumptions and methodologies of molecular genetics. A genetic understanding of disease fundamentally transforms societal views, while generating novel ethical and legal consequences. In this paper, we consider how societal understandings of nicotine addiction will be shaped by an evolving neurogenomic prism; light shining through the intersection of molecular genetics and contemporary neuroscience will further refract to determine the nature and extent of our social, ethical, legal, and policy responsibilities.

With the recent publication of a first draft of the human genome sequence, genomicization of common but complex disorders has become the latest trend (Chakravarti, 2001; Peltonen & McKusick, 2001). In contrast to genetics, which focuses on singular genes, genomics takes a genome-wide approach to explore the role of common genetic

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polymorphisms and gene expression patterns in human diseases, personality traits, and behaviors. With few exceptions (Holtzman & Marteau, 2000), many believe knowledge and technologies related to genomics will revolutionize health promotion and disease prevention (Collins & McKusick, 2001; Lander, 2000; Sander, 2000). Given the novelty of genomics research and the variety of potential applications—from gene expression profiling to genetic susceptibility testing and individual tailoring of treatment—proactive ethics and health policy research will have to rise to the challenge in imaginative ways (Kaufert, 2000).

An important task is to anticipate the impact of genomic research findings on existing medical and public health practices. Some scholars have argued that genetic information is no different from other types of health or medical information where issues of privacy, confidentiality, discrimination, and stigmatization are chief concerns. We feel that genetic information *is* sufficiently different from other health and medical information and that it deserves special consideration. We adopt this stance for several reasons.

First, the term *genetic essentialism* was suggested by Dorothy Nelkin in 1995 to describe the phenomenon whereby humans are equated with or reduced to their genetic components. Genetic essentialism may be less common among scientists and others capable of understanding that complex behaviors such as nicotine addiction are influenced by multiple genetic and environmental factors, and thus genetic testing may have minimal predictive utility or clinical significance. These complexities, however, often remain underemphasized, unnoticed, and broadly misunderstood by the public, health care providers, the media, and policy makers. As one example, preliminary interview data collected by our team shows that scientists believe that genetic bases for nicotine addiction will be polygenic, with each gene potentially having very small effects, media reports of scientific findings have suggested a "smoking gene" exists, greatly oversimplifying scientific work in this area. Although this kind of oversimplification occurs for many nongenetic risk factors for varied and complex human conditions, genetic information may be different because of widespread misunderstandings of its predictive value and thus the cultural weighting of genetic information over other types of health information.

In relation, genetic information may be unique because of the possibility of the premature translation of genetic findings into predictive tests marketed directly to consumers ahead of valid information about their clinical validity. Genetic tests for susceptibility to a certain behavior make this concern especially salient because one could infer based simply on a positive test for susceptibility that an individual actually engages in the behavior. Moreover, the public perception of genetic tests seems to be, "If I have the gene I will get the disorder," whereas in reality having the gene or genes may simply reflect a predisposition to the behavior, e.g., smoking, and many others factors (some of which may be more important than genetics) are involved that will dictate whether someone will smoke. As a result, a critical part of anticipating the impact of genomic research findings on existing medical and health practices will be paying careful attention to issues stemming from the social significance and meanings attributed to genomic information.

Although geneticists and other researchers often discuss and even use models that seek to assess the interaction of genetics and environmental influences on behavioral outcomes, these still nascent studies require further specification of phenotypes and how the environment is conceptualized. Meaning is thus important because health policies may inadvertently grant priority to certain theories of causation, e.g., privileging either a molecular or an environmental cause for complex disorders and behaviors (Lewontin, Rose, & Kamin, 1984; Parker, 1995; Tesh, 1981).

The ethical, legal, and social challenges posed by the application of genomics knowledge are beginning to be addressed (Buchanan, Brock, Daniels, & Wikler, 2001; Greely, 1998; Issa & Keyserlingk, 2000; Rothstein & Epps, 2001). In the United States, a report from the National Institutes of Health recommends that issues of behavioral genetics be made a research priority (ELSI Research Planning and Evaluation Group, 2000). In the United Kingdom, the Nuffield Council on Bioethics (2002) published the results of a working party examining the ethical issues raised by research on the genetics of behavioral characteristics.

In the field of addiction research, knowledge gained through the combined efforts of genomics, molecular biology, neuroscience, and pharmacology is expected to shed light on genetic vulnerability to addictive disorders, uncover molecular mechanisms leading to addiction, and provide the means to characterize drug-induced alterations in brain structure and function (Leshner, 1999; Nestler & Landsman, 2001). Molecular approaches play a pivotal role in human behavioral genetics and are increasingly central to psychiatric research (Rowe & Jacobson, 1999). Others have called for studies that integrate genes, brain, and behavior (Cowan & Kandel, 2001; Hyman, 2000).

From a public health viewpoint, reducing smoking and tobacco use is an unambiguous good. As a result, scientific research that offers the promise of

providing innovative strategies to facilitate this end, perhaps by enabling the development of better drug therapies, may appear at first glance to be unequivocally beneficial. A growing body of literature, however, highlights the need for an ethical analysis of public health issues and programs designed to prevent disease and promote health (Callahan & Jennings, 2002; Callahan, Koenig, & Minkler, 2000; Levin & Fleischman, 2002), including the emergent science of nicotine addiction (Hall, Carter, & Morley, 2003; Hall, Madden, & Lynskey, 2002). Building on this work, we argue that important ethical considerations must be anticipated and addressed *before* research on the neurogenetics of smoking and nicotine addiction shapes future tobacco control and prevention efforts. Only by carefully anticipating potential problems can they be avoided. Because research on nicotine addiction is still nascent, it provides an excellent case study through which to anticipate key ethical and policy issues in both behavioral genomics and the neurogenomics of addictive behaviors (Hall et al., 2002; Lerman & Niaura, 2002).

This paper has two main aims. First, we review the scientific findings that demonstrate an association between specific genetic profiles and susceptibility to smoking and nicotine addiction. When engaging in proactive ethical analysis, it is critical to intervene at the right moment, i.e., late enough in the research process that preliminary data suggesting an emerging genetic hypothesis will prove to be valid, but early enough to imagine the future implications of those findings in time for policy intervention. Second, after suggesting that the time is ripe, we explore the likely impact of the emerging science, including the ethical, legal, and social issues that will be raised by an emerging neurogenomic view of nicotine addiction and smoking behavior. Possible impacts of genetic explanations on existing policies to reduce tobacco use can be anticipated by exploring how genetic explanations may transform views of smoking and nicotine addiction with a special focus on the following three processes: medicalization, stigmatization, and individualization.

Nicotine addiction: From behavioral genetics to neurogenomics

Searching for genetic vulnerability

Family and twin studies are generally the first step in efforts to discern the relative role of genetic and environmental risk factors in the etiology of behavioral traits such as substance abuse. Family and twin studies have looked for evidence of genetic influences on smoking behavior (including smoking initiation, nicotine dependence, average cigarette consumption, smoking persistence, and inability to quit) and have estimated that genetic (vs. environmental) factors account for 40% to 65% of the variance (frequency) of tobacco use and smoking behavior (Bierut et al., 1998; Carmelli, Swan, Robinette, & Fabsitz, 1992; Cheng, Swan, & Carmelli, 2000; Heath, Kirk, Meyer, & Martin, 1999; Heath & Martin, 1993; Hughes, 1986; Kendler, Thornton, & Pederson, 2000; Koopmans, Slutske, Heath, Neale, & Boomsma, 1999; Stallings, Hewitt, Beresford, Heath, & Eaves, 1999; Swan, Carmelli, & Cardon, 1997; True et al., 1997). Taken as a whole, these studies provide compelling evidence that genetic factors explain some element of smoking behavior; however, they have neither addressed nor isolated particular genes that may be responsible for smoking behavior.

Research on the neurobiology of addiction has sought to determine which genes may affect an individual's vulnerability to nicotine addiction. Genomewide scans and other techniques to detect linkage to smoking behavior have implicated almost a dozen different chromosomes (Bergen, Korczak, Weissbecker, & Goldstein, 1999; Duggirala, Almasy, & Blangero, 1999; Straub et al., 1999). One branch of this research has explored polymorphisms (variants of genes) that may affect certain neurotransmitter pathways (specifically, dopamine, norepinephrine, GABA, and serotonin) that may play a role in predisposing an individual to nicotine addiction (Audrain et al., 1997; Bierut et al., 2000; Comings et al., 1996a; Dani & Heinemann, 1996; Heinz et al., 2000; Hu et al., 2000; Jorm et al., 2000; Koob, 1996; Lerman et al., 1998a, 1998b, 1999, 2000, 2001; Lerman & Swan, 2002; Martinez et al., 2001; McKinney et al., 2000; Noble, 2000; Noble, Berman, Ozkaragoz, & Ritchie, 1994a; Noble et al., 1994c; Pidoplichko, DeBiasi, Williams, & Dani, 1997; Pontieri, Tanda, Orzi, & Di Chiara, 1996; Sabol et al., 1999; Shields et al., 1998; Spitz et al., 1998; Sullivan et al., 2001b; Vandenbergh et al., 2002). Another branch has examined genes that may influence an individual's response to nicotine (i.e., nicotine-specific pathways), including tolerance and sensitivity to nicotine (Caporaso et al., 2001; Duga et al., 2001; Gault et al., 1998; London, Idle, Daly, & Coetzee, 1999; Oscarson et al., 1998; Perry, Davila-Garcia, Stockmeier, & Kellar, 1999; Pianezza, Sellers, & Tyndale, 1998; Sabol et al., 1999; Silverman et al., 2000; Slotkin, Pinkerton, Auman, Qiao, & Seidler, 2002). Finally, a third branch has studied genes in relation to treatment outcome (Lerman & Niaura, 2002).

Candidate genes, those hypothesized based on function to be relevant to addiction—such as genes coding for dopamine receptors—have been studied most extensively. These studies seek to show that

nicotine and other addictive drugs exert their effects through what is known as the reward (or pleasure) center of the brain, which involves the dopamine neurotransmission system (Corrigall, 1991; Dani & Heinemann, 1996; Maldonado et al., 1997; Noble, 2000; Noble et al., 1994c; Stolerman & Shoaib, 1991). Several studies have found a higher prevalence of a rare allele on the dopamine 2 receptor (DRD2) gene among smokers (Comings et al., 1996a; Noble et al., 1994c; Spitz et al., 1998), but another study (Bierut et al., 2000) did not.

Researchers also have implicated the dopamine D2 receptor in alcoholism (Blum et al., 1990; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Noble, Zhang, Ritchie, & Sparkes, 2000), cocaine addiction (Noble et al., 1993), polysubstance dependence (Smith et al., 1992; Uhl, Blum, Noble, & Smith, 1993), obesity (Noble, Noble, & Ritchie, 1994b), pathological gambling (Comings et al., 1996b), attention-deficit/hyperactivity disorder, and Tourette syndrome (Comings, Comings, & Knell, 1989; Comings et al., 1991, 1996c). Notwithstanding the various methodological issues at hand in case–control studies (Schork et al., 2001), such an array of positive associations could reflect the absence of significant findings or the need to better define the phenotype (Leboyer et al., 1998; Sher, 2000; Stoltenberg & Burmeister, 2000), or may point toward a common neurochemical basis for addictive disorders (Miller, Guttman, & Chawla, 1997), such as the recently proposed ''reward deficiency syndrome'' (Anonymous, 2001; Blum et al., 2000; Comings, 2000). Much more limited evidence is available for the dopamine D1 receptor gene (Comings et al., 1997), the dopamine D4 receptor gene (Lerman et al., 1998a; Shields et al., 1998), the dopamine D5 receptor gene (Sullivan et al., 2001b), and the dopamine transporter gene (Heinz et al., 2000; Jorm et al., 2000; Lerman et al., 1999; Lerman & Swan, 2002; Martinez et al., 2001; Sabol et al., 1999; Vandenbergh et al., 2002).

Scientists also have targeted serotonin reuptake and biosynthesis because of its role in depression and anxiety—traits often linked with smoking behavior (Blum et al., 1990). The relationship between smoking and depression is now well established (Covey, 1999; Glassman et al., 1990; Lasser et al., 2000), and its neurobiological aspects are receiving increased attention (Gamberino & Gold, 1999; Quattrocki, Baird, & Yurgelun-Todd, 2000). For example, an association among polymorphisms of the dopamine D4 receptor gene, depression, and smoking has been reported (Lerman et al., 1998a), and two recent studies suggest that neuroticism (understood by researchers as a broad personality domain that includes anxiety, depression, impulsiveness, and vulnerability) is correlated with smoking only in individuals with a specific genetic variant of the serotonin transporter gene (Hu et al., 2000; Lerman et al., 2000). Two studies have found a relationship between serotonin biosynthesis and smoking initiation (Lerman et al., 2001; Sullivan, Jiang, Neale, Kendler, & Straub, 2001a).

Results for studies of genes that affect nicotine-specific pathways, either though nicotine receptors or metabolism, have shown mixed results. Early reports suggested a role for CYP2A6, the enzyme involved in nicotine metabolism (Pianezza et al., 1998), but other studies have refuted these preliminary results (London et al., 1999; Loriot et al., 2001; Oscarson et al., 1998; Tiihonen et al., 2000). Nicotine cholinergic receptors have been shown to be important in predicting the reinforcing properties of one's nicotine response (Perry et al., 1999; Slotkin et al., 2002), but a study of four other polymorphisms found that none were associated with smoking initiation or progression to nicotine dependence (Silverman et al., 2000).

Toward a neurogenomics of addiction

Candidate gene studies are fraught with methodological difficulties, because positive allelic findings rarely withstand replication in independent case-control studies or less stratification-prone family-based samples. Developments are being made in the field of genetic epidemiology and statistical genetics regarding how to deal with stratification bias statistically. However, the vast majority of published case-control studies in the area of candidate genes and smoking have not dealt with the problem of stratification. It is instructive that the one family-based study of which we are aware (Bierut et al., 2000) did not confirm an association between DRD2 and smoking. More rigorous study designs, which will eliminate population stratification bias, are needed. One also can expect more genomewide linkage and association studies as research tools allow studies with a much higher density of markers. Genomics research on nicotine addiction will expand from the search for genetic susceptibility to fine-grained characterization of differences between normal and addicted states, the molecular explanation of the progression to addiction, and the characterization of nicotine-induced alterations in brain structure and functions.

Changes in brain gene expression patterns are thought to be key to a better understanding of tolerance, addiction, neurotoxicity, and other behavioral responses to chronic drug use (Nestler & Landsman, 2001). DNA microarray technology is emerging as a powerful tool that allows researchers to monitor simultaneously the interactions among thousands of genes involved in disease progression

and responses to pharmacological treatment (Celis et al., 2000; Rudert, 2000). These tools are beginning to be used to study drug-induced changes in the cerebral cortex (Torres & Horowitz, 1999). Although few gene expression studies have examined chronic alcoholism (Lewohl et al., 2000; Thibault et al., 2000) or nicotine exposure (Pich, Chiamulera, & Tessari, 1998; Trauth, Seidler, & Slotkin, 2000), this area of research will explode in the coming years.

Genomics seeks to establish distinctions between normal and pathological states using a nomenclature based on gene expression patterns and levels. Hence, structural and functional genomics moves the predictive enterprise from the level of genetic sequence variation to the level of gene expression. In the field of addiction, this nomenclature will integrate the individual (the genetically vulnerable brain), the addictive drug, and the environment. The brain will play a major role as the great integrator. In addition to identifying the genes involved and characterizing the molecular and neuronal features of addiction, genomics holds the promise to provide preventive smoking treatments targeted to specific individuals.

An emerging market for pharmaceutically based nicotine maintenance

Revolutions in therapeutic drug developments are what most people think about when considering the most fruitful practical applications of genomics. Pharmacogenomics seeks to improve the efficacy of medications, reduce their side effects, and ultimately optimize treatment for the individual patient (Etkin, 2000; Rusnak, Kisabeth, Herbert, & McNeil, 2001). Pharmacogenomics is viewed by some as the ultimate rational approach to pharmacotherapy, in which a patient's biological characteristics will best predict the success of a particular therapy (Evans & Relling, 1999; Roses, 2000). In contrast to pharmacogenetics, pharmacogenomics seeks to identify differences in gene expression patterns at the genome level in order to predict individual response to drugs in the treatment of various diseases (Cockett, Dracopoli, & Sigal, 2000).

While waiting for pharmacogenomics' ''proof-of-concept''—evidence that demonstrates that a treatment is efficacious—current pharmacogenetics research examines the influence of individual differences in drug-metabolizing enzymes on the efficacy and toxicity of existing medicines. In the field of addiction, pharmacogenetic research is based on the analysis of functional polymorphisms thought to influence nicotine metabolism in the liver (CYP450; Sellers & Tyndale, 2000) and polymorphisms found in genes coding for the various neurotransmitters involved in the development of addiction (Veenstra-VanderWeele, Anderson, & Cook, 2000; Wong, Buckle, & Van Tol, 2000).

The success obtained with the antidepressant bupropion in the treatment of nicotine addiction (Silagy & Formica, 2001), and the effectiveness of various molecules targeting neurotransmission systems in the treatment of alcohol and opiate dependence (Johnson & Ait-Daoud, 1999; Johnson et al., 2000), provide great incentive for developing new psychopharmacotherapies for the treatment, and possibly the prevention, of nicotine addiction. The emergence of over-the-counter nicotine delivery products—as exemplified by the Ariva lozenge (nicotine-containing dissolvable mints)—is creating a market for long-term nicotine maintenance that is being debated within the nicotine and tobacco research and control communities (Warner, Slade, & Sweanor, 1997). The promise of such varied products for long-term maintenance could encourage the pharmaceutical industry to focus on developing highly effective medicines to address individuals' needs for stimulating their brain reward functions to replace nicotine or other harmful addictive products. Other promising compounds include the antidepressant nortriptyline (Covey et al., 2000), methoxsalen (an inhibitor of CYP2A6; Sellers, Kaplan, & Tyndale, 2000), tranylcypromine (an antidepressant and inhibitor of monoamine oxidase A; Fowler et al., 1996), and vigabatrin (an inhibitor of nicotine-induced dopamine release; Dewey et al., 1999).

Genomics and tobacco control: A double-edged sword

Even before any genomic tests or neuropharmacotherapies are developed, the insights gained through the combined efforts of genomics, molecular biology, neuroscience, and pharmacology to understand the biological basis of nicotine addiction could trigger important transformations in public and health professionals' views of smoking. These views could further shape practices and policies to prevent and treat nicotine addiction and to reduce tobacco use. Because most tobacco control efforts are aimed at individual choice to use tobacco, the emerging neurogenomic understanding of nicotine addiction, which could situate tobacco use farther from the realm of choice, will have important social consequences, creating ethical challenges and shaping policy debates about tobacco control measures and public health and medical intervention to reduce tobacco use.

How are neurogenomic explanations of nicotine addiction likely to be articulated with the concepts of causality, responsibility, choice, and free will, and thus to influence existing health polices? Whereas a significant body of social science research has addressed the links between disease causality

and moral responsibility in common disorders (Crawford, 1985, 1994; Lupton, 1993; Sachs, 1996; Williams, 1998), few studies have looked more specifically at the role of genetic causes (Marteau & Senior, 1997) or at concepts of responsibility and risk management in the context of behavioral genetics (Anderson, 1994; Parker, 1999). Some observers suggest that a renewed focus on the biological bases of behavior threatens our understanding of free will and responsibility, which are at the core of democratic societies (Blank, 1999).

Several analysts have stressed the difficulty of isolating the genetic contribution to complex disorders, cautioning that naïve biological deterministic interpretations are likely to promote the misuse of genetic explanations in public policy, in the courts, in the heath insurance industry, and in medical practice (Bailey, 1997; Botkin, McMahon, & Francis, 1999; Carson & Rothstein, 1999; Kaplan, 2000; Parens, 1996). A recent example of this occurred in 2000 when the Burlington Northern Santa Fe Railroad Company began secretly conducting genetic tests of some of its workers who had sought worker's compensation and medical attention for carpal tunnel syndrome. The tests were designed to find a mutation in a gene called PMP 22, which causes a person to be susceptible to nerve injury from pressure, stretching, or repetitive use and can lead to carpal tunnel syndrome. The workers, who settled out of court, contended that Burlington Northern conducted the tests to avoid financial responsibility for treating or compensating the workers' carpal tunnel conditions.

Although the seriousness of these considerations is likely to depend on the degree of causative effect attributed to genetic variants, popular media reports that tend to overstate the evidence of genetic factors in complex behaviors in general (Conrad, 1999), and of smoking in particular (Byars, 1998; Elias, 1999; Haybron, 1998; Ritter, 1998, 1999), give substance to these concerns. We can begin to address the possible impact of genomic explanations on existing practices and policies to reduce tobacco use by exploring how genomic explanations are likely to intersect with the social processes of medicalization, stigmatization, and individualization of smoking.

From bad habit to brain disease: The medicalization of smoking

Conceptualizations of smoking in the scientific literature, which are evolving, will necessarily provide the essential foundations for designing research strategies and interventions to reduce tobacco use. Once considered a bad habit, smoking is now generally understood as an addiction (Benowitz, 1999). The dependence on nicotine that results from using tobacco was formally recognized in the 1988 U.S. surgeon general's report (U.S. Department of Health and Human Services [USDHHS], 1988). More recently, smoking has been referred to as a "pediatric disease," because smokers often become addicted at an early age (Kessler, 1995; Woolf, 1997), and drug addictions (including addiction to nicotine) are increasingly characterized as a "disease of the brain" (Kosten, 1998; Leshner, 1997; Wise, 2000).

The concept of medicalization refers to the processes by which the labels *healthy* and *ill* are made relevant for more and more aspects of human life (Zola, 1972). Medicalization, however, does not simply reflect increased medical control over private and public life, but rather a conceptual shift whereby a complex social phenomenon is now recognized and understood as a health problem, requiring medical intervention. Behavior is often recognized as deviant before it becomes medicalized (Conrad & Schneider, 1980), and smoking is no different in this respect. Since the mid-1970s, smoking has been perceived as a socially unacceptable, deviant act (Markle & Troyer, 1979). North American antismoking movements, especially in California, have succeeded in pushing smoking toward the margins, fostering an image of smoking that is increasingly seen as an unhealthy, foolish, and irresponsible behavior.

The classic drawback of medicalization is its reductionism, which places excessive emphasis on the biological and individual determinants of disease at the expense of a more holistic perspective that emphasizes the social, cultural, and environmental contributions to disease and illness (Conrad, 1992). In the example of smoking, a doctor or nurse assisting an individual to quit smoking is expected to address the physiological and psychological symptoms of dependence while focusing less on the environmental situations (e.g., stress or peer pressure) that contribute to smoking behavior and difficulty in quitting or on the political dimensions (e.g., government subsidies of tobacco production) that are not within the purview of clinicians.

The medicalization of smoking began when causal links were established between tobacco use and diseases, including lung cancer, heart disease, and chronic respiratory problems (U.S. Department of Health, Education, and Welfare, 1964). In the 1980s, smoking was recognized as fostering both psychological and physiological dependence (wherein the former is often understood as addiction and the latter as dependence). For example, the 1988 surgeon general's report defined smoking as an addiction to nicotine, effectively drawing a conceptual link between smoking and addictions to illicit drugs such as cocaine (USDHHS, 1988). Moreover, the inclusion of tobacco dependence in the *International Classification of Diseases* (World

Health Organization, 1992) and the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994) contributes to the conceptualization of smoking as a disease, the symptoms of which are considered treatable problems, further reinforcing medicalization and legitimizing professional intervention.

Impact of neurogenomic explanations on views of smoking and on practices and policies to reduce tobacco use

Neurogenomic explanations of nicotine addiction will contribute to the view that smoking and nicotine addiction stem from an underlying neurotransmission system imbalance, a reward deficiency syndrome, or more generally a brain addictive disorder. Moreover, neurogenomic explanations may be able to provide predictive information on an individual's biological vulnerability to addiction, the likelihood of developing psychiatric comorbidities, or the likelihood of responding successfully to particular psychopharmacotherapies.

Neurogenomic explanations of nicotine addiction also have the potential to shift clinical treatment of smoking and nicotine addiction dramatically by allowing for predictive biological information on the nature of an individual's addiction and possible responses to available treatments. This could result in the categorization of smokers according to an underlying neuromolecular status, vulnerability, or response. It also could generate public and professional understandings of the biology or psychology of groups perceived to be or truly at higher risk of developing addiction (e.g., individuals with particular ancestry). Finally, it could highlight a potentially stigmatizing biological susceptibility to addictive disorders that may exist among individuals who are not (yet) suffering from brain addictive disorders.

Neurogenomic explanations suggest a similarity between nicotine addiction and other drug addictions, and that addiction is a brain disorder or disease. A growing number of studies using performance tests or brain imaging techniques have begun to describe and characterize cognitive dysfunctions among individuals afflicted with addictive drug disorders (Grant, Contoreggi, & London, 2000; Jentsch & Taylor, 1999; London, Ernst, Grant, Bonson, & Weinstein, 2000; Lyvers, 2000; Rogers & Robbins, 2001; Volkow & Fowler, 2000). For example, frontal cortex dysfunctions observed among drug users are used to explain, and provide biological support for, the "loss of self-control," the "compulsive" behavior, or the "impaired performance in decision making" considered psychiatric hallmarks of addictive behaviors. However, the lack of intoxicating effects of nicotine and the improvement of certain cognitive functions such as learning and memory associated with nicotine intake (Ernst, Heishman, Spurgeon, & London, 2001; Heishman, 1999) suggests that the comparisons between tobacco use and the use of other addictive drugs may be limited. Neurogenomic explanations may either clarify or blur the distinction between nicotine addiction and other drug addictions that lead to an erosion of personal autonomy and even criminal behavior.

For those who conceptualize nicotine addiction as a disease, the smoker has little control over nicotine intake and needs special intervention to quit (via nicotine replacement or other pharmacotherapies). Even though quitting cold turkey has been the most popular method of quitting, this method may not work for all smokers. The medicalization of addiction upholds the belief that addicts are the passive agent in a disease process over which they have no control. If medicalization is generally acknowledged, then health practitioners would have a duty both to prevent the addiction and to mitigate its sequelae.

For those who conceptualize smoking as a habit that can be broken by sheer will, smoking is a choice. In this model, smokers can be viewed as living in denial, as unable to care for themselves, or as suffering from mental weakness (or lack of will) that makes quitting difficult. In these instances, biomedical interventions provided by individual health care professionals have less of a role and some interventions could be viewed as paternalistic. Whereas drugs can be viewed and are used as an adjunct to help people modify their behavior, prescribing drugs that interfere in brain processes also may take away an individual's free will or autonomy, even if people take these drugs voluntarily. For example, if there were a drug to help smokers quit that worked by disrupting the brain reward pathway, it also could disrupt other activities and feelings that have nothing to do with smoking.

Individualization: Challenges to traditional public health campaigns

One of the greatest challenges in tobacco control is getting prevention and treatment strategies disseminated, adopted, and implemented. According to the surgeon general's latest report on smoking, broader implementation of existing treatment methods could produce a more rapid and larger short-term impact on tobacco-related health statistics than any other component of a comprehensive tobacco control effort (U.S. Department of Health and Human Services, 2000). However, smoking cessation is still not widely integrated into health care practice (Thorndike, Rigotti, Stafford, & Singer, 1998) nor is it always covered by health insurance (Curry,

Grothaus, McAfee, & Pabiniak, 1998; ''Smoking cessation services,'' 1999).

However, recent surveys show that smoking is no longer seen solely as a public health problem but also as a chronic disease, amenable to biological and physiological manipulation and treatment. Health care providers are increasingly recording the smoking status of their patients, giving advice to quit or reduce consumption, and providing assistance for quitting (McEwen & West, 2001). Such medicalization may ultimately lead physicians and health payers to provide the necessary evaluation and treatment of smokers (Steinberg & White, 1996).

The focus on the addictive properties of nicotine has provided solid bases for developing new strategies for tobacco control (Heishman, Kozlowski, & Henningfield, 1997) and for promoting the medical treatment of tobacco dependence (Slade, 1999). For example, the effort to define the cigarette as a ''device'' containing a ''drug'' (nicotine) has had a significant impact on policies to reduce tobacco use and in 1996 prompted the U.S. Food and Drug Administration to consider cigarettes and smokeless tobacco as products under its jurisdiction (Kessler et al., 1997).

Targeting individuals or specific groups as more likely to become regular smokers or having more difficulty quitting because of some genetic risk factors is in sharp contrast to existing public health approaches that focus on access to the vector (the cigarette), and on the various environmental and institutional mechanisms by which tobacco exposure is maintained, such as advertising and other forms of promotion. The rhetoric of individualization through genomic explanations of smoking may be used to shift responsibility for the addiction away from the cigarette and on to individuals' genetic make-up. Highlighting the biological susceptibilities to addiction could individualize the problem of smoking, and genetic explanations of smoking could be used to jeopardize mass-oriented public health strategies that focus on preventing or reducing tobacco exposure.

Neurogenomic understandings and the further medicalization of smoking

Genomic explanations of nicotine addiction will reinforce the trend toward the medicalization of smoking and of smoking cessation interventions. Medicalizing smoking could affect smokers' understandings of the health risks associated with their behavior, their perception of the nature of their addiction, and their perception of the need for medical assistance in quitting. Individualized genetic information or neurogenomic assessment of their vulnerability to nicotine addiction or smoking-related diseases, e.g., through brain imaging and other biochemical and genetic tests, may lead to a decrease in ''self-exempting beliefs'' that smokers have about the health consequences of smoking (Chapman, Wong, & Smith, 1993). A hope exists, unproved to date, that knowledge of disease risk tailored to the individual will lead to heightened compliance with recommended preventive regimens or avoidance of risky behavior. Whether genomic explanations will foster a view of nicotine addiction as a treatable disease or trigger fatalistic attitudes is critical and remains to be seen.

Careful consideration must be given to findings from genomic and neuroscience research that highlight the connections and common pathways among psychiatric diseases, addictive disorders, and smoking behavior. Although such research may eventually help to predict the clinical efficacy of certain smoking cessation drugs by identifying smokers who are more responsive to psychotropic medications, the association of smoking with a host of ''mental vulnerabilities,'' although not a new finding (Cohen, 1988), is now clothed with a biological mantle likely to cast additional stigma on smoking and smokers. Pleiotropy of genetic susceptibility testing—genes are rarely associated with a single outcome—raises ethical questions about screening, particularly of children and adolescents. In this context, smokers may be reluctant to seek medical care for their nicotine addiction if they fear their behavior will be labeled as a psychiatric problem.

Stigmatization: Genetic etiology and social identity

Stigmatization of smoking. Over the past 40 years, public health advocates have put major efforts toward reducing the prevalence of smoking, resulting in significant reduction of smoking and consequent health benefits. The antismoking campaigns now serve as models of successful public health movements (Nathanson, 1999) and have relied explicitly on the stigmatization of smoking and smokers as an effective strategy to bring about changes in health behaviors.

Stigmatization is mostly understood in connection with the negative consequences it brings to individuals and groups. According to Goffman (1963), stigma is ''an attribute that is deeply discrediting'' and that reduces the bearer ''from a whole and usual person to a tainted, discounted one'' (p. 3). The community sanctions that can result from stigmatization can take many forms, from reduced access to certain goods to job discrimination. Moreover, in contemporary Western industrialized cultures, stigma typically attaches to ''achieved disorders'' (i.e., disorders for which people are considered culpable). In other words, more negative social

response is associated with behaviors whose onset is believed to be under individual control.

Often given a pejorative connotation, the process of stigmatization is not always negative. It can be understood as a power negotiation among social groups to introduce changes or to reinforce social stability (Ben-Yehuda, 1990). Stigmatization of domestic violence contributes to the public perception that a man who beats his wife commits a socially reprehensible act. Stigmatization of this type of behavior contributes to promoting respect for women and equality between men and women. Similarly the stigmatization process associated with smoking and tobacco control strategies was brought about to counteract the glamorous image of smoking presented in magazines and movies. Stigmatization must then be interpreted as a process of imposing one group's view of smoking (that of health advocates) over another group's view (that of the tobacco industry, advocates of free speech, and some smokers) to initiate a substantial change in health behavior. Because of the dynamic dimension of this social negotiation process, stigmatized behaviors vary across cultures and with time.

Consequences of stigmatization of smoking on smokers. Stigmatization of a behavior such as smoking is inevitably also a process of stigmatization of the smokers themselves, even if "for their own good" or to protect the health of "innocent others." The stigmatization of smokers and their isolation, owing to restrictions on space where smoking is allowed, has marginalized smoking in some states (e.g., California) and countries. This strategy has had at least two negative consequences: increased appeal of smoking among authority-questioning youth and diminished respect for smokers that may translate into actions that reduce smokers' equality of opportunity in society.

For example, several reports suggest that physicians and medical trainees justify rationing of health care and scarce medical procedures, such as care in intensive care units or organ transplant, to smokers on the basis that patients have contributed to their own diseases (Allmark, 1995; Levenson & Olbrisch, 1993; Marshall, Kramer, Lewiston, Starnes, & Theodore, 1990; Miller et al., 1995). In a survey of the general population in the United Kingdom, smoking stigma and discrimination against smokers appeared to be related to prejudice against various racial, religious, and political groups (Allmark, 1995). In a study of the relationships between racial discrimination and cigarette smoking among Blacks in the United States, those who experienced frequent discrimination had a much higher smoking prevalence rate than those who experienced infrequent discrimination (26.7% vs. 6.4%, respectively; Landrine & Klonoff, 2000).

Analyses of recent tobacco advertisements suggest that the tobacco industry is taking the stigmatization of smoking seriously, using it to its own benefit. Since 1997, tobacco companies have used a new advertising strategy that depicts smoking as a celebration of stigma by painting smoking as an act of defiance and by mocking the moral and discursive foundations of antismoking claims (Brown, 2000). Whereas the stigmatization of smoking may work to reduce adult smoking behavior, the moral loading of smoking may increase the seductiveness of smoking among youth. As Katz (1997) notes, "while the adult nonsmokers and ex-smokers of our society have had a secular moral field day with labeling, ostracism, and outright hostility toward smokers, the adolescent youth, typically sensitive to the 'injustices' and social labeling this movement has created, have taken up smoking" (p. 328). As one example, Glantz (2003) has argued that the frequency of smoking depictions in top-grossing movies in the United States has returned to levels not seen since 1950 (well before popular understanding that smoking was a major cause of disease) and has almost doubled since 1990, creating a major public health problem. His concern is supported by a recent study showing strong evidence of a link between viewing smoking in movies and smoking initiation among adolescents (Dalton et al., 2003).

With "healthy" lifestyles and behaviors equated with a "secular state of grace" (Leichter, 1981), those with unhealthy lifestyles and behaviors, of which smoking is an example, are relegated to a subclass of individuals who cannot or will not conform to appropriate moral ideals. Perhaps the most poignant example of the stigmatization of smokers are reports indicating that lung cancer victims—whose numbers exceed those with breast, prostate, and colon cancer combined—face social censure rather than compassion (Epstein, 1998). It will be important to assess what effect, if any, these attitudes may have on clinical care and research dollars for smoking-related diseases.

The most troubling aspect of the climate of good health as moral virtue, however, is what it does to smokers themselves. Because smoking is legal, smokers are presumably entitled to the same constitutional rights as others, perhaps with the exception of where and when they smoke. However, smoking status is already affecting employability. Leichter (1997) notes that "Cable News Network (CNN) will not hire smokers; U-Haul, and Baker Hughes, Inc., of Houston, Texas, fine employees who smoke *while not* on the job; and one company, Ford Meter Box Company of Wabash, Indiana, fired an employee when she tested positive, in a urine test, for nicotine" (p. 362).

The impact of a neurogenomic understanding of nicotine addiction on stigmatization

Forces leading to decreased stigma. Analyses of the impact of genetic etiology on disease and stigma, which have looked mainly at single gene disorders, suggest that genetic causes might be associated with fatalistic attitudes. However, in the context of common multifactorial disorders, the genetic contribution is only a fraction of what might be involved in pathogenesis. Even in familial hereditary forms of common disorders, such as cardiovascular disease or cancer, the genetic contribution to the overall risk profile of an individual, however important, is believed to be modifiable by attempts to reduce environmental (mostly lifestyle) risk factors. A neurogenomic understanding of nicotine addiction may overemphasize one's biological vulnerability, which lies outside of one's control, and usher in a more compassionate attitude toward smokers.

The availability of nicotine-containing products that do not entail the same health risks as tobacco products introduces a fundamental change in the context of tobacco control policy and is likely to inform our response to addictive behaviors. If individuals can get nicotine without exposing themselves (and others) to a delivery device that causes major and deadly diseases, how should society respond to those nicotine addicts? Is it possible that these individuals are taking no more risks than those addicted to, say, caffeine?

By suggesting a fundamental basic neurochemical process involved in all addictive behaviors, neurogenomic explanations may suggest that the reasons why some addictive behaviors are socially acceptable whereas others are not have to do with the social consequences rather than the addiction per se. The brain, like other parts of the body, will be seen as capable of enhancement and, when coupled with the concomitant recognition of the brain's modes of adaptation and plasticity, could increase the social acceptability of biological manipulation with food, vitamins, herbal supplements, and socially acceptable psychoactive substances, including psychopharmacology.

Forces leading to increased stigma. Although widespread belief remains that the onset of smoking results from a personal choice, neurogenomic explanations of nicotine addiction have the potential to radically transform beliefs about initiation of smoking in the near future. If neurogenomic explanations provide predictive knowledge about susceptibility to addiction, such knowledge might contribute to an increase in self-responsibility to make the "right" choice. Instead of promoting fatalism, neurogenomic explanations of smoking, and most likely all genomic explanations associated with complex multifactorial diseases or behaviors, may foster a duty to know and to avoid engaging in risky lifestyles. For smokers who might not have benefited from early knowledge about genetic susceptibility, the later divulgence about their own neurogenetic contribution to the smoking behavior could suggest a duty to get the appropriate evaluation and treatment to stop smoking.

Most likely, however, a genetic etiology could both diminish and reinforce the stigma associated with smoking, and different interest groups will use this knowledge to promote their own agendas. The recognition of a genetic contribution to stigmatized conditions such as obesity may reduce stigma, by shifting responsibility for the disorder away from individuals' lifestyle choices, or presumed lack of will, and onto their biology, over which they presumably have no control. Based on a similar rationale, some observers believe that behavioral genomics research will contribute to improved public perception and tolerance of mental disorders, freeing behavioral genomics research from the ethical concerns associated with genetic labeling (McGuffin, Riley, & Plomin, 2001). Although genomic explanations are likely to be welcomed by health professionals, there might be social resistance to this biological perspective, especially if it is interpreted as reducing smokers' responsibility for their smoking.

Smoking has become increasingly marginalized in North American society, reflecting the success of the current sociopolitical dynamic promoting the stigmatization of smoking, a strategy integral to smoking control policies (Goldstein, 1991; Goodin, 1989; Gusfield, 1993; Markle & Troyer, 1979). The effects of stigmatization may be both positive and negative. One effect may involve victim blaming, but stigmatization also is an efficient and beneficial process for changing social norms when the stigmatized behavior is clearly unacceptable or poses important public health risks (Ben-Yehuda, 1990).

Because of documented differences in drug response for people of different ancestry or continental origins (Sellers, 1998), population stratification according to racial background is becoming an important methodological issue in pharmacogenetics and, more generally, in all human genetic sequence variation research. In one study, authors have reported that a genetic variant associated with the risk of smoking was observed only in those of African, as opposed to European, ancestry (Shields et al., 1998). Other investigations indicate that individuals with African ancestry metabolize nicotine differently than people of other populations, which some investigators hypothesize may account for why African Americans have more difficulty quitting and are more prone to lung cancer (Caraballo et al., 1998;

Pérez-Stable, Herrera, Jacob, & Benowitz, 1998). One immediate concern is that providing a genetic explanation for racial differences in nicotine metabolism could lead to further stigmatization of already marginalized groups of smokers on the grounds that something inherent put them at higher risk of becoming smokers or being unable to quit. Furthermore, identification of a susceptibility to nicotine addiction may lead some individuals to consider certain human populations as somehow inherently weak or damaged or prone to mental illness.

Although stratification according to race is ubiquitous in biomedical research, particularly in epidemiology, tying notions of difference to genetic variations among human populations is potentially more harmful because it attributes difference to an inherent and seemingly immutable (genetic) characteristic of an individual. Historical evidence uncovers the social harms related to beliefs about genetic differences among people of different continental origins. Attributions of a spoiled or diseased identity generally reflect broader social prejudice; the classic example is denial of admission to the U.S. Air Force Academy to African Americans heterozygous for the sickle cell anemia gene (Duster, 1990). The claim that the blood of candidates with African ancestry was more likely to sickle at high altitudes was scientifically flawed yet was adopted as social policy.

If a genomic understanding of nicotine addiction proves to be associated with a higher risk of suffering from mood disorders, depression, or other psychiatric comorbidities, then genetic labeling may create additional stigma by calling into question a person's capacity for self-control and, most controversially, for autonomous decision making. Although perhaps not representing mainstream thought, some researchers feel that genetic research will provide the tools for finding the ultimate underlying causes, and the nature of the causal links, between addictive behaviors and psychiatric comorbidities (Waldman & Slutske, 2000). For these researchers, social and environmental links appear less creditable by comparison. More recently, others have called for more transdisciplinary research that involves concurrent expertise beyond that of genetics (e.g., Swan & Lessov, in press), which will be important for addressing all of the causes of smoking and nicotine addiction.

Future applications: Looking beyond technological hurdles

Given the complexity of human behavior and addictive disorders (Owen, Cardno, & O'Donovan, 2000), it is unlikely that a single gene with major causal effect will be found to confer susceptibility to smoking. Hence, simple and definitive predictive or diagnostic genetic testing (such as tests for Huntington disease) are not likely to be developed. As for hereditary forms of cancers, neurodegenerative disorders, and cardiovascular disease, it is possible that clinically relevant genetic susceptibilities will be identified only in a small percentage of highly dependent smokers with a family history of addictions. Supporting this hypothesis, some researchers speculate that as social pressure increases against smoking, the proportion of hard-core smokers, whose addiction may be more likely to originate from biological susceptibilities, will increase (Pomerleau, 1995). Others, however, have speculated that hard-core smokers encounter more stressful environments, invoking an environmental causation (e.g., Emery, Gilpin, Ake, Farkas, & Pierce, 2000, Warner & Burns, 2003).

If genetic tests become available, whether to assess response to pharmacological treatment or susceptibility to addictive behaviors, important policy questions will nevertheless arise: Will health insurers be willing to offer genetic testing to help tailor smoking cessation? Will genetic testing be mandatory to ensure smokers' access to smoking cessation programs based on claims that testing makes programs more cost-effective? If new psychotropic drugs targeted at the various neurotransmitter pathways are developed, careful consideration of the consequences of manipulating neurophysiological functions will be needed, whether such pharmacotherapy is used curatively (to assist in smoking cessation) or to prevent individuals or groups at high risk from becoming regular smokers. Although the nicotine "vaccines" currently in clinical trials have been developed independent of current genetic research, if researchers were able to develop genetic tests for susceptibility to nicotine, these tests could be used to determine who might benefit from the administration of a nicotine vaccine. Vaccines raise yet other issues including the parameters for their usage, given that they could be targeted at healthy people and minors.

Conclusion

Although scientists and policy analysts might disagree on exact timing or potential utility, tobacco control interventions based on genomic knowledge *are* being developed. We believe that a proactive, comprehensive analysis of emerging applications must address the value and meanings of genetic information, as well as their scientific validity. While awaiting confirmation of the role of specific genes or gene complexes in nicotine addiction, biomedical researchers seem confident that genomics will lead to fruitful discoveries that will advance understanding of complex behaviors such as nicotine addiction.

This paradigm of explanation—and the resulting neurogenomicization of our views about smoking—will have an impact regardless of whether the research lives up to current expectations.

Although the precise nature of genetic findings and their implications remains hypothetical, the genomics revolution will inevitably affect policies to reduce tobacco use, along with other domains of medical practice and public health. The possible impact of genomic explanations on existing policies to reduce tobacco use can be anticipated by exploring their intersection with three social processes: medicalization, individualization, and stigmatization. Given that some genetic variants under study have different prevalence rates among human populations with diverse continental origin and that most candidate genes under study are also potentially linked to an array of behaviors—including other addictions, personality traits, and some mood and psychiatric disorders—careful consideration must be given to the social meanings of neurogenomic explanations of nicotine addiction. By beginning now to address these issues, ethical dilemmas may be anticipated and possible policy approaches delineated, rather than simply reacting as the science unfolds.

Bearing in mind the tentative nature of genetic findings, it is premature to address specific applications of this research or to outline comprehensive recommendations. It is not too soon, however, to begin the broad dialogue that must accompany behavioral genetic research in general and research on smoking and nicotine addiction in particular. The Nuffield Council on Bioethics (2002) and the Hastings Center report (2004) have highlighted important scientific limitations and ethical issues arising from research in behavioral genetics. We share their belief that genetics contributes to our overall knowledge of human behavior by complementing, not displacing, other ways of understanding human behavior. However, we echo their concern that the promise of research in human behavioral genetics may be overstated, given the difficulty of defining traits, the complexity of heritability estimations, and the myriad social and environmental influences on behavior. Ethical red flags include the medicalization of certain behaviors or ways of being, reduced social tolerance of previously "normal" traits, and the potential for increasing inequality across human groups.

Translation of basic research into clinical medicine and public health practice will require careful, detailed, and thorough evaluation of the benefits, burdens, and risks of gene-based interventions (e.g., Koenig, Greely, McConnell, Silverberg, & Raffin, 1998; McConnell, Koenig, Greely, & Raffin, 1999). We make the following recommendations:

1. Smoking is a complex and multifaceted human behavior. Genetic research on nicotine addiction should consider smoking in the context of its meaning for those who smoke and the broader social, cultural, political, and economic context of smoking and nicotine addiction. Further research is needed. For example, does knowledge of a genetic contribution make it more or less likely that smokers will want to quit? Would such knowledge affect the tolerance that nonsmokers have toward secondhand smoke? Would knowledge of genetic research make a difference to insurers and health care providers in the support of smoking cessation services? Would the research programs of nicotine and tobacco scientists be altered, given knowledge of genetic involvement? How will commercialization affect the translation of scientific findings about genetic influences into clinical or public health practice?
2. The potential value of genetic approaches to understanding and controlling nicotine addiction should be considered alongside current public health and tobacco control efforts to reduce smoking prevalence and tobacco-related disease. Reducing the public health burden of smoking is an important goal that will have both environmental and biological solutions. Genetics will no more offer a complete answer for reducing the smoking burden than do current public health and tobacco control efforts. As genetic research unfolds, it will be important to assess the efficacy and impact of this research and its potential clinical applications against other available strategies to reduce tobacco-related diseases.
3. Given the potential for misuse and misunderstanding of scientific research, public presentation of genetic findings must be carried out with utmost care. Echoing a recommendation made by the Nuffield Council on Bioethics, researchers have a duty to communicate their findings in a responsible manner. Announcements of "*the* gene for smoking" are all too common in the popular media. One way to improve communication is to hold briefings to help guide journalists' interpretations of emerging research. Researchers can provide information on the scientific findings and their limitations, as well as the next steps in scientific inquiry.
4. We encourage an ongoing dialogue among stakeholders involved in formulating tobacco control policy; discussions should address the benefits and limitations of neurogenomic approaches to smoking control, considering how best to use this emerging body of research responsibly and sensitively. We suggest devoting

a portion of the annual meeting of the Society for Research on Nicotine and Tobacco to a discussion of the ethical, social, and legal implications of genetic research on smoking behavior.

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