

Vested Interests in Addiction Research and Policy

'To prove this is the industry's best hope': big tobacco's support of research on the genetics of nicotine addiction

Kenneth R. Gundle¹, Molly J. Dingel² & Barbara A. Koenig³

Harvard Medical School, Boston, MA, USA,¹ Center for Learning Innovation, University of Minnesota, Rochester, MN, USA² and Mayo Clinic, Rochester, MN, USA³

ABSTRACT

Background New molecular techniques focus a genetic lens upon nicotine addiction. Given the medical and economic costs associated with smoking, innovative approaches to smoking cessation and prevention must be pursued; but can sound research be manipulated by the tobacco industry? **Methodology** The chronological narrative of this paper was created using iterative reviews of primary sources (the Legacy Tobacco Documents), supplemented with secondary literature to provide a broader context. The empirical data inform an ethics and policy analysis of tobacco industry-funded research. **Findings** The search for a genetic basis for smoking is consistent with industry's decades-long plan to deflect responsibility away from the tobacco companies and onto individuals' genetic constitutions. Internal documents reveal long-standing support for genetic research as a strategy to relieve the tobacco industry of its legal responsibility for tobacco-related disease. **Conclusions** Industry may turn the findings of genetics to its own ends, changing strategy from creating a 'safe' cigarette to defining a 'safe' smoker.

Keywords Genetics, legacy tobacco documents, tobacco industry.

Correspondence to: Barbara A. Koenig, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: koenig.barbara@mayo.edu
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INTRODUCTION

The field of molecular genetics is transforming research on the etiology of smoking behavior and nicotine addiction [1,2]. Novel technologies allow researchers to perform genome-wide association studies that produce suggestive findings [3]. If molecular approaches are to be utilized to complement treatment and public health efforts with the goal of decreasing smoking-related disease, there is a need to examine the emergence of a genetic understanding of smoking among stakeholders in smoking and tobacco control. It is vital that the perspectives of the tobacco industry—a key stakeholder—be assessed.

The tobacco industry has long recognized the potential of genetic explanations to minimize its legal responsibility for tobacco-related disease, and has been aware of and pursued such justifications since the 1950s. Efforts to capitalize on this potential were, in the past, hampered by another industry strategy: denial of the addictive quali-

ties of nicotine. The tobacco documents made available from the Minnesota tobacco trial and the resulting settlement of that case present an opportunity to gain insight into industry knowledge and support of research on the genetics of nicotine addiction [4]. As Glantz and colleagues showed in a pioneering 1995 analysis of the tobacco documents, industry-funded scientists studied the addictive qualities of nicotine actively while company leaders denied it [5]. Now that the tobacco industry is modifying its hard-line denial of the addictive nature of nicotine [6,7], it may turn its attention from creating a 'safe' cigarette to defining a 'safe' smoker. Genetic studies could undergird such a strategy.

Constructing an historical narrative of the tobacco industry's evolving position on the genetics of smoking behavior provides a basis for anticipating future industry tactics. In this paper, we use an analysis of the Legacy Tobacco Documents to illustrate how the search for a genetic basis for smoking behavior is consistent with industry's decades-long plan to deflect social

responsibility away from the tobacco companies and onto individuals' genetic constitutions (see Appendix S1 in the online version of this paper for a description of methods).

THE NARRATIVE

The long shadow of R.A. Fisher

In response to an accumulating body of research linking smoking to lung cancer [8,9], the British Medical Research Council in 1957 issued 'Tobacco Smoking and Cancer of the Lung', a report that states: '... a major part of the increase [in lung cancer] is associated with tobacco smoking' and 'the relationship is one of direct cause and effect' [10]. These findings were questioned by R.A. Fisher, a renowned statistician and geneticist, marking the first time the tobacco industry paid attention to genetics. The story of Fisher's role as a consultant for the Tobacco Manufacturers' Standing Committee can be found online in Appendix S2.

The tobacco industry capitalized on Fisher's reputation and outspoken advocacy of a genetic explanation linking smoking behavior and cancer. Dr George L. Saiger, a consultant paid more than \$50 000 by the tobacco industry between 1965 and 1970 [11–13], testified at both the 1965 and 1969 Congressional Hearings on the health effects of smoking. He stressed that Fisher's constitutional hypothesis was a plausible alternative to claims that smoking caused cancer, saying:

There is strong reason to believe that the constitutional hypothesis fits the evidence appearing in the Report of the Surgeon General's Committee [the original 1964 Surgeon General's report [14]] at least as well as the cigarette hypothesis... More research would be necessary to test definitively the strength of one hypothesis against that of the other [15].

Fisher's constitutional hypothesis became a critical part of the tobacco industry's strategy to deny the negative effects of cigarettes by promoting 'controversy' and providing other possible explanations for the scientific data [16].

From Fisher's constitutional hypothesis to behavioral genetics

The Legacy documents reveal that the tobacco industry undertook two separate lines of research to bolster the credibility of the constitutional hypothesis: that one or more genes affect a person's risk for lung cancer, and that at least some of the same genes influence whether people become smokers. The latter component of the Fisher hypothesis—that genes influence smoking behavior—is a

question that now falls under the rubric of behavioral genetics.

In 1962, during a lawsuit against the American Tobacco Company [17], a new interpretation of the association between smoking and lung cancer was presented to company lawyers [18]. This internal paper, written by American Tobacco Company President Robert Karl Heimann and a consultant, analyzed previously published data [19–21] on the smoking habits of American Tobacco Company's Richmond, Virginia employees. American Tobacco employees had been reported to smoke at a rate twice that of the general United States population, yet in more than 14 years the mortality rate of more than 11 000 employees from all causes (including cancer) was 30% lower than the general population [22]. This result contrasted with numerous other surveys of smoking and lung cancer rates, and one goal of this internal paper was to reconcile these findings.

While the 1964 Surgeon General's report explained the discrepancy in findings based on a healthy worker bias (i.e. as some categories of sick or debilitated people in the population are not employed, it is inaccurate to compare a disease prevalence in a work-force to the general population) [[14], p. 182], President Heimann and his co-author provided a different interpretation, that: 'excessive smoking may be diagnostic of other factors predisposing to higher mortality rates' [22]. They hypothesized that heavy smokers are 'excess-prone' (see Appendix S3 online for full description). The tobacco industry representatives argued that their analysis of the published data showed that it was not cigarettes that caused lung cancer, but a third element (namely, genetic makeup) that caused people to both 'take risks' (excess smoking, eating, etc.) and develop lung cancer.

However, this paper was not published because the American Tobacco Company lawyers feared that the opposition could use the results of this analysis against them [18]. While this new study postulated an explanation for lung and other cancers that does not blame smoking, it did not prove a causal relationship and could turn court battles into a question of whose theory was superior [[16], p. 441; [23]]. Industry lawyers also thought it unwise for the manufacturers to support a paper that argued that smoking excessively indicates poor health, even if it does not cause it. This paper was withheld from publication, although Edward S. Harlow, Managing Director of Research and Development, expressed regret at the decision to shelve a promising alternative explanation [24]. However, the data on American Tobacco Company employees continued to be used to cast doubt on a causal link between smoking and cancer by providing a sample of people who smoked heavily but had lower rates of cancer than the general population.

The 'excess-proneness' model of smoking behavior was revisited in 1972 when Fred R. Panzer, Vice President of Public Relations for the Tobacco Institute, wrote a memo ('The Roper Proposal') [25] in response to a suggestion by Burns (Bud) W. Roper, an expert on public opinion polls, who recommended researching people's 'excessivity' [25]. Panzer's memo is an often-cited document on the tobacco industry's strategy detailing the plan of 'creating doubt of the health charge without actually denying it' [25]. According to Roper's hypothesis, if someone is driven psychologically and/or physiologically to over-smoking, over-drinking, etc., then this life-style of excess may contribute to an early death. If validated, Roper contended, 'The focus would change from *one product* to a *type of person*' [emphasis in original] [26]. Panzer saw a 'credible alternative' to the causal theory in the connection between a theory of excess and the constitutional hypothesis. The public, Panzer wrote, 'must perceive, understand, and believe in evidence to sustain their opinions that smoking may not be the causal factor' [25]. Roper's idea, grounded in the constitutional hypothesis, gave Panzer confidence: 'It is my strong belief that we now have an opportunity to take the initiative in the cigarette controversy, and start to turn it around'.

Roper's data were used, therefore, to support a constitutional hypothesis. For example, a correlation between divorce and smoking was explained in an internal Philip Morris memo [27]: 'Our position, of course, is neither that divorce causes the smoking nor that the smoking causes the divorce, but that both tendencies proceed from common constitutional factors relating to the difficulty of making a smooth adaptation to the life situation'. Behaviors relating to smoking and divorce were seen as the result of one's genetic make-up [27].

Panzer's sole criticism of the Roper Proposal was that it was not 'strictly scientific' [25]. Whether searching for 'excess-proneness' or 'hereditary tendencies', a scientific strategy to 'take the initiative in the cigarette controversy' would not present itself to the tobacco industry for several more years.

Tobacco industry research on the genetics of nicotine addiction

From the 1950s into the 1970s, the tobacco industry's evolving defense against the causal theory of smoking leading to lung cancer or poor health increasingly made use of scientific research. Both the developing field of behavioral genetics and the idea of excess proneness became an area of special interest to the tobacco industry. In 1954 the industry published a 'Frank Statement' to the American public and created the Tobacco Industry Research Committee (TIRC), which was nominally

intended to provide research addressing the 'smoking and health controversy'. The TIRC, subsequently renamed the Council for Tobacco Research (CTR), served as part of a public relations strategy to promote controversy and refute the unhealthy impact of tobacco [4]. The initial critique by Fisher, epidemiological work by Heimann, and a later survey by The Roper Organization were a part of this effort to fund research to counter the growing body of evidence in support of a causal link between smoking and a host of diseases. The idea that smokers and non-smokers are constitutionally different was a cornerstone of the industry's argument, but a rigorous scientific means to advance this position was unavailable.

This changed with the advent of behavioral genetics. Edwin Jacob, a tobacco industry lawyer who managed secret 'special projects' that funded scientists to produce results that supported the industry's positions, comments in a 1974 internal report that 'it has become increasingly apparent that constitutional hypotheses merit massive investigation' and 'At present, happily, newly developed research knowledge and techniques—especially in genetics—provide the possibility of much more extensive and promising exploration of the constitutional hypothesis than has heretofore even been conceivable' [28]. The tobacco industry capitalized on the advances being made in genetics with the intent of bringing new hope to their research and legal defense strategies.

In the mid-1970s, a group of researchers approached CTR with a proposal to study the genetics of 'smoking behavior'. A 1974 draft of the study, entitled 'Genetic and Environmental Basis of Tobacco-related Behavior', describes its research questions:

Specific research questions will include: (1) Is it possible to demonstrate unequivocal genetic involvement in smoking behavior? (2) What is the relative magnitude and nature of the genetic control? (3) Is it possible to determine the genetically influenced neurophysiological and pharmacological correlates of tobacco-related behavior? (4) Is it possible to discriminate between smokers and non-smokers without reference to smoking behavior [29]?

The fourth question has the same research goal as previous work on excess-proneness: what separates the smoker and the non-smoker, apart from smoking? This 1974 proposal explicitly states that the purpose is to test the Fisher hypothesis: 'Data obtained from investigations into these questions should contribute substantially to understanding one aspect of the "Fisher hypothesis"—the hereditary influence on smoking behavior. In addition, we shall eventually be able to address the total hypothesis directly' [30]. The plan was to first determine

a hereditary influence on smoking, and then attempt to show a linked hereditary influence on disease.

Three related projects were proposed: (1) a human study using populations in Hawaii to be conducted by Dr Geoffrey C. Ashton; (2) animal studies using mice to be conducted at the Institute of Behavioral Genetics (IBG) of the University of Colorado, with Dr Gerald E. McClearn as principal investigator; and (3) studies using twins from the Swedish Twin registry under the guidance of Dr David W. Crumpacker, also of the University of Colorado.

The proposed coordinator of the three components was McClearn, who in 1967 established the IBG in Colorado and was its first director. McClearn and the IBG were at the forefront of behavioral genetics [31], and McClearn was the President-elect of the Behavioral Genetics Association when the first proposal was submitted to the CTR in 1974 [32]. The CTR Scientific Advisory Board recognized that McClearn's alcohol studies 'seem[ed] successful in leading to important and new concepts and biological interpretations' [33] and that McClearn's animal study was a chance to test the Fisher hypothesis: 'It is a remarkable opportunity to find out the degree of genetic influence upon the smoking habit or nicotine . . . [I]f some part of the smoking public inherits this tendency, and their medical data are collected, the facts would likely revolutionize the general scientific attitude in this field' [34]. Sommers also focused upon the ability of this work to 'provide a base of knowledge to build on', and set the foundation for further advances on the genetics of smoking behavior [34]. Proposed projects were given separate grades for 'merit' and 'relevance' by reviewers, and Sommers gave this work an 'A' for both.

CTR leaders acknowledged that this study conveyed both benefits and risks to the tobacco industry. The deficiency of the animal study was that: 'This proposal is essentially a study of the biological and behavioral responses of mice to nicotine. The assumption is that nicotine may be habituating or addictive, or that genetic differences in tolerance may exist and may be identified or found' [33]. At this time the tobacco industry maintained publicly that nicotine was not addictive, although internal memos indicate the industry had been aware of the addictive nature of nicotine for more than 15 years [4]. While this avenue of research may validate the Fisher hypothesis, investigating a genetic propensity to nicotine addiction could be seen as contradicting the industry's stance that nicotine is not addictive.

The potential conflict over nicotine may have been one reason this study was proposed as a CTR 'Special Project' [35]. Using these Special Projects, industry lawyers supported research that could refute the relationship between smoking and disease or continue to encourage controversy [16]. In a confidential memo, industry lawyers wrote: 'CTR Special Projects instead were prima-

rily a means of attracting researchers to areas of scientific inquiry not being addressed and, in particular, were focused on satisfying the needs of lawyers involved in defending the tobacco industry in litigation' [36]. Proposing research on the genetics of smoking behavior as a CTR Special Project suggests that industry lawyers thought the work would be helpful in litigation defense.

Edwin Jacob's 1974 report on Special Projects for the tobacco industry expressed support for the IBG studies 'with the conviction that, for the first time, the Tobacco Industry has available, within realistic compass, the scientific means to carry out a major investigation of the constitutional hypothesis' [28]. In March 1975, at a meeting on industry-sponsored research, the work of McClearn was addressed specifically [37]. Two industry lawyers were present, including David R. Hardy of the law firm Shook, Hardy, and Bacon [38]. Commenting on the Fisher hypothesis, Hardy said, 'to prove this is the industry's best hope'. Drs Gardner and Sommers, who attended the meeting, agreed. Both the animal study and the Swedish twin study were approved [39].

While both McClearn's animal study and Crumpacker's research using the Swedish Twin Registry were funded by the CTR, Ashton's Hawaii population study was not. In 1993, the *Wall Street Journal* reported: 'Dr Ashton says the lawyer told him "the presidents of the tobacco companies had turned down the proposal because they didn't think the outcome would be useful to them"' [40]. Not denying this statement, industry lawyers responded in a draft press statement: 'A response to this "allegation" is probably unnecessary. The claim however, could be used to support our arguments about the purposes of the CTR Special Projects and to rebut the argument that CTR Special Projects were how the industry funded "adverse" research it might want to "hide"' [36]. In contrast to Aston's (unfunded, potentially 'adverse') research study, the IBG studies at the University of Colorado were seen as potentially beneficial to the industry's position by investigating the constitutional or Fisher hypothesis, and represented Special Projects that would not be construed as 'hidden' or 'adverse' research.

Papers from the IBG were mentioned in CTR Annual Reports from 1976 until 1983. These Annual Reports listed abstracts for published papers completed with CTR support, and were sent to physicians, researchers, tobacco industry leaders and others throughout the world. McClearn received more than \$530 000 in support of his mouse studies between 1976 and 1979 [41–43]. During the same period, Crumpacker received more than \$550 000 in funding for work with the Swedish Twin Registry [44–46], in part developed originally to study the genetics of smoking behaviors and smoking-related disease [47].

Dr Allan C. Collins also emerged as a major researcher of the genetics of nicotine addiction at the IBG. Collins joined the faculty at the University of Colorado in 1972, and developed mouse models for studying the genetics of smoking behavior. Successful site visits prompted the CTR to praise Collins and support funding for his work. From 1978 to 1981, Collins received more than \$150 000 from the CTR for research on the genetics of smoking behavior in mice [48,49].

By the 1980s the idea that smoking behaviors may have a genetic component had begun to enter the scientific mainstream. Tobacco industry funding of researchers such as Crumpacker, McClearn and Collins contributed to the development of this field. In 1983 Collins wrote a letter thanking CTR 'for providing the funding that allowed us to get a solid start in this area', and suggested that he would be able to obtain funding from the National Institute on Drug Abuse (NIDA) to continue the research [50]. These researchers, differently motivated than industry leaders, sought elucidation and testing of hypotheses in behavioral genetics. However, any NIDA-funded research by Collins and others could not be conducted with planning, direction and oversight by industry personnel. To this end, an R.J. Reynolds internal memo included recommendations that this work be re-funded directly by Reynolds [51]. Between 1986 and 1994, and apparently independent of CTR, R.J. Reynolds' extramural research funding to Collins was in excess of \$700 000 to continue basic research on the genetics and neurobiology of nicotine response and addiction [52–56].

In 1995, at the first annual meeting of the Society for Research on Nicotine and Tobacco, there was a symposium entitled 'Genetic Influences on Nicotine Dependence'. Both Collins and McClearn were featured in this symposium and have been honored for their groundbreaking research [57–62]. A paper published in *Addiction* describes the meeting, including the presentation of Collins' research on mouse strains and McClearn's work from quantitative genetic theory, concluding that: 'Evidence from several lines of research suggests that the use and effects of nicotine or tobacco smoking is influenced in part by genetic factors' [63]. A legal representative for Brown and Williamson attended the conference and reported that the genetic work was 'the most significant scientific session of the meeting' [64].

Regardless of the scientific motivations or intent of the scientists involved, the research was funded by an industry that felt it had much to gain from work upholding a genetic basis of tobacco dependence. Although one could argue that all research stems from and is funded by 'interested' parties, we suggest that tobacco industry funding is of particular concern because of the large body of research documenting the tobacco industry's activities:

denying publicly but accepting privately the addictive nature of nicotine [4]; holding 'judicial seminars' designed to influence court rulings [65]; using scientific knowledge to create products that were increasingly addictive [66]; and paying scientists to speak publicly in an attempt to keep controversy alive regarding passive smoking (second-hand smoke) [67,68]. That tobacco industry lawyers have both directed much of the industry-sponsored research and stifled 'unfavorable' studies speaks to the extreme nature of the bias in this body of research.

Our 21st-century perspective is, of course, informed by these revelations; but we must use extreme caution in evaluating the actions of behavioral genetics researchers who accepted industry funding in the 1970s. It would be both unfair and inappropriate to judge their actions by today's standards. It was only in the mid-1980s that suspicions about tobacco industry activities began to raise concerns among university-based researchers, who asked: is accepting industry funding ethical [S. Glantz, personal communication]? By 1995, condemnation of tobacco industry funding of research was voiced widely, including recommendations published in the *Journal of the American Medical Association* [69]. Our historical account is not meant to suggest that pioneering behavioral genetics researchers were violating ethical norms when they sought funding from the tobacco industry. Explicit standards condemning such funding have been established only with the passage of time, and in an era of declining funding, whether to accept support from the tobacco industry remains a matter of considerable dispute.

ADDICTIONS GENETICS TODAY: PAST AS PROLOGUE

Much as Collins predicted, research conducted by the tobacco industry laid the ground-work for subsequent research in the genetics of smoking behavior funded by NIDA and other groups. Genomic approaches to combating drug use are now a priority at the National Institutes of Health [70,71]. NIDA and other scientists investigating genetic bases of smoking behavior often justify this research with the hope that their research will not only increase our understanding of the neuroscience of tobacco dependence, but also complement traditional public health programs through the development of novel smoking cessation therapies, treatments that will reduce smoking-related disease [72]. For example, several leading researchers stated in *Science* in 2004: 'Employing the power of genetic studies in understanding the underlying biological, behavioral, and environmental factors will enhance research on etiology, treatment, and prevention for these complex diseases' [72]. In 2007, many of

the same authors reiterate in the *Journal of the American Medical Association* that: 'An important rationale for genetic studies is that the identification of novel neurobiological pathways could result in more effective treatments of nicotine dependence' [73]. Others have argued strongly that traditional public health interventions, not genetic research, will prove to be more cost effective way to achieve this goal [74]. For example, a recent Institute of Medicine report highlights the value of population-based strategies such as increased taxes and indoor smoking bans [75,76]. In the background of this seemingly straightforward policy debate is the powerful influence of the tobacco industry, which has for decades sought to use genetic information for its own profit. If new molecular approaches to addiction are to be deployed in the interest of public health it is vital to anticipate future tobacco industry tactics, which can be accomplished by looking at past actions as well as contemporary trends. Policy scholars have raised similar concerns about the food industry, arguing that it is important to heed the lessons of 'Big Tobacco' when evaluating the actions of 'Big Food's' role in combating the obesity epidemic [77].

From the 1960s until the early 1970s the tobacco industry studied and promoted the idea of a 'safe cigarette' [[16], p. 108–31] in an attempt to minimize concerns about the health risks of smoking. This strategy included deception about decreased nicotine and tar levels in 'light' cigarettes [78]. Similarly, the tobacco industry has had a long-standing interest in creating a cigarette that is perceived to be addiction-free. In a 1980 Tobacco Institute memo, Paul K. Knopick, editor of the Institute's newsletter, writes of a warning by industry lawyers that: 'the entire matter of addiction is the most potent weapon a prosecuting attorney can have . . . We can't defend continued smoking as a "free choice" if the person was "addicted" ' [79]; but what if, instead of an addiction-free cigarette, the industry could promote an 'addiction-free' smoker? Evidence of non-dependent smokers, or 'chippers', already exists in the literature [80,81]. This 'addiction-free' smoker would be making an 'informed choice' to smoke, and therefore could not hold the tobacco industry liable for damages resulting from 'addiction'. The tobacco industry can argue that the genetic revolution, including genetic research not funded by the industry, is confirming what they have long known: that a crucial component of nicotine addiction is genetic and that there is a small number of people who should not smoke, but for the vast majority of people cigarettes are a product that can be used in a responsible and voluntary way [A. Brandt, personal communication].

Just as with 'light' cigarettes, such a campaign would be a deception. Anyone who smokes would still be subject to negative health effects and, for most of the population,

repeated cigarette use creates at least some level of dependence [82]. Yet neither of these facts would necessarily prevent the spread of a *belief* in safe-smoking, or addiction-free smoking, for at least some portion of the population. If it were shown conclusively that some people have a genetic make-up that protects them from tobacco dependence, the tobacco industry might incorporate this sentiment in promotional materials aimed at younger smokers, who are more likely to underestimate how hard it is to quit when they are experimenting with smoking. Some recent marketing campaigns indicate that the tobacco industry is trying to appeal to chippers: flavored cigarettes featuring tin-cans with colorful party scenes or dissolvable tobacco-laden pellets or strips that are packaged to look like mints are marketed to social smokers—especially those who like to smoke while drinking. The promotion of 'chipper' smoking, a concept the tobacco industry may promote with genetic research, could be a growth market for the industry in the 21st century.

Lessons for researchers

The tobacco industry's agenda in promoting the notion of 'addiction-free' smokers is at odds with goals of genetic researchers who hope to understand more clearly the biology of addiction or provide new and better targeted therapies for tobacco dependence. It is critical to ask what strategies might scientists take to keep their work from being co-opted for the tobacco industry's gain. Although this is a complex issue with no simple answer, two strategies to mediate this co-option are to: (1) avoid industry funding and (2) use caution when publicly communicating results or interacting with the media about genetic studies. Both strategies rely on scientists' cultivating a heightened awareness of potential misuse of their work.

It is well documented that biomedical research often yields results favorable to industries funding that research. Funding sources may influence study design, hypothesis formulation, interpretation of results, whether a study is actually published and how well it is disseminated [83–89]. Bias remains even when controlling for methodological quality, statistical power, magnitude of treatment effect and blinding procedures [90–92], which indicates that even well-intentioned research may produce biased outcomes. As we argued above, problems of bias are particularly acute for research funded by the tobacco industry because of its well-documented history of suppressing unwelcome research evidence and its role in publicly denying what it admitted privately—that its products are addictive and carcinogenic. Further, within the tobacco control community, serious questions exist about the validity of any research funded by tobacco industry monies [93,94].

Avoiding industry funding helps scientists to distance themselves from the improprieties of the tobacco industry and ensures that their results remain independent of industry influence. Leading medical journals, such as the *Journal of the American Medical Association* and the *New England Journal of Medicine*, will not knowingly publish research funded by the tobacco industry [95].

Secondly, scientists should be cautious about how they communicate their findings to the public, avoiding the tendency for easy soundbites. Headlines touting ‘gene for smoking identified’ can be avoided through careful work with journalists if scientists emphasize that *all* smokers are at risk for addiction and tobacco-related disease. Reports about genetic findings could also highlight the critical role of the social environment—and particularly the tobacco industry’s massive marketing activities—in promoting smoking. Regardless of any individual’s genetic susceptibility to becoming addicted to exogenous nicotine, there would be no epidemic of tobacco-induced addiction, disease, and death without the tobacco industry’s aggressive design of the product to maximize its addictive potential together with massive marketing and promotion [96].

It is also important to recognize that unanticipated results inevitably follow from public and governmental efforts to hold the tobacco industry responsible. Scholars have documented the ways in which tobacco industry efforts that appear to further public health goals actually benefit the industry itself. For example, industry anti-smoking advertisements may actually *encourage* teens to smoke [97]. Furthermore, efforts to control the industry’s influence or hold them accountable for the health burden of tobacco-related disease may backfire. Allan Brandt argues that, in the United States, the Master Settlement Agreement has benefited the industry in unexpected ways. The settlement not only spared the industry from further costly litigation but also, to ensure their share of settlement funds, prompted states to defend the market shares and financial viability of the largest tobacco companies. In addition, public health programs did not experience the expected benefits from an infusion of settlement funds [96].

Final thoughts

With the completion of the Human Genome Project in 2003 and the rise of molecular genetics as a research tool to investigate the neurobiology of complex behaviors such as smoking, many scientists and clinicians have high hopes that greater understanding of the mechanisms underlying nicotine addiction will yield new and better-targeted therapies, decreasing drastically the incidence of smoking-related disease. While we endorse these hopes, we must keep another probable scenario at the

forefront of policy deliberations. Based on the narrative we have presented, the tobacco industry is poised to use genetic research to achieve its long-term goal: an alternative understanding of smoking that will help the industry shed the aura of ‘death-peddling Big Tobacco’ and place the blame for smoking squarely on an individual’s genetic constitution.

Declarations of interest

K.R.G. and M.J.D: none. Dr Koenig served previously without financial compensation on the Affymetrix Corporation ethics advisory board. Dr Koenig is a co-principal investigator on a study entitled: ‘A Proof-of-Principle Trial of Communication to Patients Receiving Predictive Genomic Risk Assessment’ that is funded jointly by Navigenics, Inc. and Mayo Clinic. She receives no personal compensation from Navigenics.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Methods: searching the legacy documents.
Appendix S2 The long shadow of R.A. Fisher [full version].

Appendix S3 ‘Excess proneness’.

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