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ETHICAL ISSUES IN CONDUCTING BEHAVIORAL GENETICS RESEARCH: THE CASE OF SMOKING PREVENTION TRIALS AMONG ADOLESCENTS*

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I. INTRODUCTION

Despite decades of clinical research and concentrated public health efforts, smoking remains the leading cause of preventable death in the United States.¹ Most adult smokers begin smoking before the age of 18,² and two-thirds of adolescents engage in smoking behaviors.³ A substantial proportion of these adolescents exhibit symptoms consistent with nicotine addiction.⁴ Thus far, efforts to prevent smoking and to help adolescents quit smoking have been met with limited success,⁵ leading to the need for broader, trans-disciplinary approaches⁶ to

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1. J. Michael McGinnis & William H. Foege, *Actual Causes of Death in the United States*, 270 JAMA 2207, 2207 (1993).

2. OFFICE OF SMOKING AND HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS), PREVENTING TOBACCO USE AMONG YOUNG PEOPLE: A REPORT OF THE SURGEON GENERAL, 65 (1994).

3. According to recent studies, 64% of adolescents report ever having smoked cigarettes, 28% report having smoked on at least one day in the past month, and 14% report having smoked on at least 20 of the last 30 days. Cf. Lloyd D. Johnson et al., *Monitoring the Future, Nat'l Results on Adolescent Drug Use: Overview of Key Findings*, 2001 NAT'L INST. ON DRUG ABUSE, NIH PUB. NO. 02-5105, U.S. DHHS (2002); CENTER FOR DISEASE AND CONTROL (CDC), *Trends in Cigarette Smoking Among High School Students—United States, 1991-2001*, 51 MORBID. & MORT. WKLY. REP. 409, 409-12 (2002), available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5119a1.htm (last visited Nov. 12, 2002).

4. See Warren R. Stanton, *DSM-III-R Tobacco Dependence and Quitting During Late Adolescence*, 20 ADDICT. BEHAV. 595, 598 (1995); Suzanne M. Colby et al., *Measuring Nicotine Dependence Among Youth: A Review of Available Approaches and Instruments*, 59 SUPPL. 1 DRUG & ALCHOL. DEPEND. S23, S24 (2000).

5. See, e.g., Steve Sussman et al., *Effects of Thirty-four Adolescent Tobacco Use Cessation and Prevention Trials on Regular Users of Tobacco Products*, 34 SUBST. USE & MISUSE 1469, 1469 (1999).

understanding the etiology of smoking behavior and the mechanisms of response to treatment.

While much has been learned about the socio-environmental and psychological determinants of adolescent smoking, recent attention has been devoted to understanding the role of genetic factors. Genes related to dopaminergic and serotonin pathways, as well as genes related to nicotine metabolism, contribute to the tendency to smoke and the ability to quit smoking.⁷ Current research focuses on furthering the understanding of genotype/phenotype relationships for smoking behavior.⁸ Studies that address the role of genetics in smoking behavior in adolescents, but do not provide information on genetic status to study participants and are ongoing.⁹ There also have been proposals to test adolescents for susceptibility to smoking related health consequences.¹⁰ Additionally, genetic tests for nicotine dependency are currently being marketed to parents on the Internet.¹¹

Because of the enthusiasm to prevent and treat adolescent smoking, and the progress in genetics research, one can anticipate, in the near future, a growing interest in conducting clinical research that uses genetic information in conjunction with other strategies to affect smoking behavior, or to select the optimal treatment and/or prevention interventions for individuals based on their genetic profiles.¹² Such clinical research, whether treatment intervention trials in smokers or

6. Richard R. Clayton et al., *Hutchinson Smoking Prevention Project: A New Gold Standard in Prevention Science Requires New Transdisciplinary Thinking*, 92 J. NAT'L CANCER INST. 1964, 1965 (2000).

7. The understanding of the role of genetic factors in smoking behavior and response to treatment is very tentative at this point, but several large scale, well-designed studies are under way that may clarify and validate preliminary findings about the relationship between particular polymorphisms and specific smoking phenotypes. Additional research will be needed to understand the function of these genetic variants, and the complex interactions between genes, social and environmental factors, as well as individual personality traits. Caryn Lerman & Wade Berrettini, *Elucidating the Role of Genetic Factors in Cigarette Smoking Behavior and Nicotine Dependence*, 2002 AM. J. MED. GENE. 5, 5 (NEURO-PSYCHIATRIC GENETICS) (in press).

8. *Id.*

9. See, e.g., Janet Audrain et al., *Recruiting Adolescents into Genetic Studies of Smoking Behavior*, 11 CANCER EPIDEMIOL. BIOMARKERS & PREV. 249 (2002).

10. See generally T. Thelin et al., *Primary Prevention in a High-Risk Group: Smoking Habits in Adolescents with Homozygous Alpha-1-Antitrypsin Deficiency (ATD)*, 85 ACTA. PAEDIATRIS 1207 (1996).

11. See, e.g., DOC BLUM, *Neutraceuticals for the Millennium*, available at <http://www.docbluminc.com/smoking.htm> (last visited Dec. 17, 2002).

12. One possible strategy, could be to use genetic information to tailor pharmacological smoking cessation treatment by genotype (i.e., bupropion or transnasal nicotine spray). Another strategy might be to incorporate information on genetic predisposition to becoming addicted to nicotine or being at increased risk for smoking related health complications, as part of comprehensive smoking prevention programs aimed at adolescents who have not yet started smoking; See, e.g., Caryn Lerman et al., *Pharmacogenetic Investigation of Smoking Cessation Treatment*, 12 PHARMACOGENETICS 627 (2002); see Thelin, *supra* note 10.

prevention intervention trials in non-smokers, will raise ethical concerns regarding the assessment of benefits and risks to participants, particularly because of the complexity of the association between environmental/genetic factors and behavior, and the stigmatizing potential of information that may be generated as part of some of these studies.¹³

An assessment of the benefits and risks depends, in part, on the type of participants to be included. A central ethical issue raised by the prospect of conducting clinical research that involves disclosure of genetic information to participants is whether these studies should exclude or specifically target adolescents.¹⁴ While there has been support for involving adolescents in research related to smoking on ethical grounds,¹⁵ the specific issues related to research that provides genetic information to participants have not been thoroughly addressed. There has been a recent shift in federal policy to include “minors” (children and adolescents) in research (or justify their exclusion) because of the growing appreciation of a profound lack of data about safety and efficacy of pharmaceuticals and other interventions in children.¹⁶ In the specific case of clinical research that incorporates genetic information into smoking intervention programs, there are two arguments for at least *including*, if not targeting, adolescents.¹⁷ One argument, which is only relevant when considering the involvement of adolescents in smoking *prevention* trials, is that because the vast majority of smokers begin smoking in adolescence, targeting smoking prevention

13. The same genes currently associated with smoking behaviors have been associated with other addictive behaviors, and other behavioral conditions. See, e.g., D.E. Comings et al., *Homozygosity at the Dopamine DRD3 Receptor Gene in Cocaine Dependence*, 4 MOLECULAR PSYCHIATRY 484 (1999); Sachio Matsushita et al., *Association Study of Serotonin Transporter Gene Regulatory Region Polymorphism and Alcoholism*, 105 AM. J. MED. GENETICS 446 (2001); Ernest P. Noble, *The DRD2 Gene in Psychiatric and Neurological Disorders and its Phenotypes*, 1 PHARMACOGENOMICS 309 (2000).

14. In this paper, we do not mean to distinguish between adolescents and children according to age. As long as the “minor” is at increased risk of initiating smoking behavior, they would be eligible to participate in smoking prevention trials, although we might want to set a minimum age (e.g., 10) to maximize the likelihood of informed assent. Even above the minimum age, the “minor” is likely to have a different level of involvement in the informed consent process if s/he is 11-years-old than if s/he is 15-years-old.

15. See, e.g., Eric T. Moolchan & Robin Mermelstein, *Research on Tobacco Use Among Teenagers: Ethical Challenges*, 30 J. ADOLESCENT HEALTH 409 (2002).

16. The National Institutes of Health (NIH) issued a policy requiring the inclusion of children in “all human subjects research conducted or supported by the NIH,” unless there are scientific or ethical reasons to exclude them. NIH POL’Y AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RES. INVOLVING HUM. SUBJECTS (1998), available at <http://grants1.nih.gov/grants/guide/notice-files/NOT98-024.html> (last visited Nov. 11, 2002). The Food and Drug Administration (FDA) also encourages pediatric research, by mandating that pharmaceutical firms include children in studies of all relevant indications. See 21 CFR §§ 201.23, 314.55 (2002). The FDA also offers six months additional market exclusivity for data pertaining to the use of tested agents in children. See 21 U.S.C.A. § 355a(b)(1)(A)(i) (2002), and see also Robert Steinbrook, *Testing Medications in Children*, 347 N. ENG L. J. MED. 1462, 1462 (2002).

17. See *supra* note 14.

studies on adolescents is an efficient, strategic use of public resources and has the greatest potential to reduce the public health burden of smoking.¹⁸ The second argument, which is relevant to either *prevention or treatment* trials, is that from a scientific perspective, the physiological, psychological and social characteristics of adolescents are sufficiently different from those of adults that it may not be reasonable to generalize from studies of adults to adolescents.¹⁹

There are also two main arguments for *excluding* adolescents from smoking prevention or intervention trials until there is more information from studies of adults. The first argument is that, when there is insufficient information about the likelihood or magnitude of medical and social risks associated with the disclosure of genetic information to participants, research should initially be conducted in adults. This concern about exposing children to unknown risks is supported by the National Commission for the Protection of Human Subjects, which recommended that research be conducted on adults before it is done in children, when appropriate, because children are a *vulnerable* population.²⁰ The concern about the vulnerability of children as research participants is related to their limited ability to provide informed consent due to their cognitive and emotional development, level of autonomy, and dependence on family influence.²¹ The vulnerability of children is particularly important in research that provides genetic information because the degree of risk, in this case social risk, is unknown. Even in the case of genetic testing for susceptibility to adult onset disease (as opposed to behavioral traits),

18. Among adults who smoke, 82% first smoked before the age of 18, and 53% became daily smokers before 18 years of age. See *supra* note 2 at 65. In this paper, we are not addressing the possibility of prevention trials for older adults or treatment trials of "minors" because these target populations do not account for the largest public health burden. Therefore, from the perspective of public health resources, the impact of such trials is not likely to be worth the investment. See *infra* note 69 tbl. 1.

19. See generally Ellen A. Skinner et al., *Children's Beliefs About Control, Means-Ends, and Agency: Developmental Differences During Middle Childhood*, 11 INT'L. J. BEHAV. DEVEL. 369 (1988); Lawrence D. Cohn et al., *Risk Perception: Differences Between Adolescents and Adults*, 14 HEALTH PSYCHOL. 217 (1995); John S. Murray, *Conducting Psychosocial Research with Children and Adolescents: A Developmental Perspective*, 13 APPL. NURS. RES. 151 (2000).

20. NAT'L COMM'N FOR THE PROTECTION OF HUM. SUBJECTS OF BIOMEDICAL AND BEHAV. RES., REPORT AND RECOMMENDATIONS: RES. INVOLVING CHILDREN, PUB. NO. (OS) 77-0004, WASHINGTON, D.C.: U.S. PRINTING OFFICE 1-2 (1977).

21. Robert J. Levine, *Adolescents as Research Subjects Without Permission of Their Parents or Guardians: Ethical Considerations*, 17 J. ADOLESCENT HEALTH 287, 288 (1995); John S. Santelli et al., *Guidelines for Adolescent Health Research: A Position Paper of the Society for Adolescent Medicine*, 17 J. ADOLESC. HEALTH 270, 272 (1995). See generally R.M. Nelson, *Children as Research Subjects*, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 47 (J.P. Kahn et al., eds., 1998); Lois A. Weithorn & David G. Scherer, *Children's Involvement in Research Participation Decisions: Psychological Considerations*, in CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS AND LAW 133 (M.A. Grodin & L.H. Glanz eds., 1994).

where more is known about the relative benefits and risks from studies of adults, testing of children and adolescents is highly controversial.²²

The second argument derives from a larger question, which is relevant to adults as well, of whether clinical research that uses individual genetic information to reduce smoking-related morbidity and mortality should be privileged over other research strategies to influence smoking behavior. According to this argument, efforts aimed at modifying the social environment experienced by adolescents should take precedence over genetic-based efforts because such interventions would potentially benefit all adolescents, not just those identified as having certain genetic traits and/or involved in interventions. Also, environmental approaches would not pose the same social risks as those associated with genetic testing for complex behaviors, such as stigmatization and/or discrimination against teens identified with specific smoking associated genetic variants.

In this paper, we argue that clinical research that assesses the impact of genetic information on smoking behaviors should be conducted in adults before it is conducted in adolescents. While we support the trend of greater inclusion of children and adolescents in research, at this time, there is insufficient data about expected benefits to justify the potential risks of involving adolescents in prevention trials that use information about genetic susceptibility to nicotine addiction. This paper presents the evidence of limited benefit and potential risks to adolescents who might participate in such studies, as well as challenges to adolescents' ability to engage in an informed and voluntary decision-making process regarding their participation in clinical research that uses genetic information to influence smoking behavior. We begin with a general discussion of benefits and risks, and proceed to their specific application in the case of adolescents. We then review current debates regarding adolescents' capacity to provide informed consent.

22. Unless genetic tests offer direct medical benefits, the inability of children to provide informed consent has resulted in a tendency to defer decisions about genetic testing until adulthood. *See, e.g.,* ASHG Social Issues Committees, *ASHG/ACMG Report, Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents*, 57 *AM. J. HUM. GENET.* 1233 (1995); Theresa M. Marteau, *The Genetic Testing of Children*, 31 *J. MED. GENET.* 743 (1994); Dorothy C. Wertz et al., *Genetic Testing for Children and Adolescents: Who Decides?*, 272 *JAMA* 875 (1994); Ellen Wright Clayton, *Removing the Shadow of the Law From the Debate About Genetic Testing of Children*, 57 *AM. MED. GENE.* 630 (1995); Eric D. Kodish, *Testing Children for Cancer Genes: The Rule of Earliest Onset*, 135 *J. PEDIATRICS* 390 (1999).

II. ASSESSMENT OF BENEFITS AND RISKS OF ENROLLING ADOLESCENTS IN PREVENTION TRIALS

A. Questionable Benefit

Any expectation of direct benefit to participants depends on the prior evidence of a relationship between genes and smoking related outcome/behavior (clinical validity) and the impact of this information on behavior (clinical utility).²³ The evidence for a relationship between genes and smoking behavior includes twin studies that suggest the proportion of variance in smoking accounted for by heritable factors ranges from about 50% for smoking initiation to about 70% for the progression to nicotine dependence.²⁴ Recently, molecular genetic approaches have been utilized to study genes in the dopamine reward pathway including receptor genes, transporter genes and metabolism genes. Although some studies have suggested associations of smoking behavior with genetic variants in the dopamine pathway,²⁵ these findings have not been consistent.²⁶ Other studies have linked genes in the serotonin pathway to the likelihood of smoking initiation and the age at which smoking begins.²⁷

The potential benefit of utilizing genetic information in clinical research studies requires consideration of the robustness of these genotype/phenotype relationships.²⁸ The understanding of complex genotype/phenotype associations is tentative, at best, because the necessary studies of the relationship between genes and behavior are in their infancy. Thus, it is not clear whether genetic information about smoking behaviors is sufficiently certain to be used in clinical research.

Furthermore, the impact of knowing one's genetic predisposition on behavior change is unclear. Behavior change could be motivated by the use of information

23. See generally Wylie Burke, *Genetic Testing*, 347 N. ENGL. J. MED. 1867 (2002).

24. See, e.g., A.C. Heath & N.G. Martin, *Genetic Models for the Natural History of Smoking: Evidence for a Genetic Influence on Smoking Persistence*, 18 ADDICT. BEHAV. 19 (1993); Kenneth S. Kendler et al., *A Population-based Twin Study in Women of Smoking Initiation and Nicotine Dependence*, 29 PSYCHOL. MED. 299 (1999); Patrick F. Sullivan & Kenneth S. Kendler, *The Genetic Epidemiology of Smoking*, 1 NICOTINE & TOB. RES. S51 (1999).

25. See, e.g., Sue Z. Sabol et al., *A Genetic Association for Cigarette Smoking Behavior*, 18 HEALTH PSYCHOL. 7 (1999), available at www.apa.org/journals/hea/hea1817.html (last visited Nov. 17, 2002); Caryn Lerman et al., *Evidence Suggesting the Role of Specific Genetic Factors in Cigarette Smoking*, 18 HEALTH PSYCHOL. 14 (1999).

26. See generally Laura Jean Bierut et al., *Family-Based Study of the Association of the Dopamine D2 Receptor Gene (DRD2) with Habitual Smoking*, 90 AM. J. MED. GENETICS 299 (2000); Anthony F. Jorm et al., *Association of Smoking and Personality with a Polymorphism of the Dopamine Transporter Gene: Results from a Community Survey*, 96 AM. J. MED. GENETICS 331 (2000).

27. See generally Patrick F. Sullivan et al., *Association of the Tryptophan Hydroxylase Gene with Smoking Initiation but not Progression to Nicotine Dependence*, 105 AM. J. MED. GENETICS 479 (2001) (citing Caryn Lerman et al., *Tryptophan Hydroxylase Gene Variant & Smoking Behavior*, 105 AM. J. MED. GENETICS 518 (2001)).

28. Lerman & Berrettini, *supra* note 7 at 10-11.

about genes associated with smoking behaviors, or about genes associated with greater disease susceptibility among individuals who smoke.²⁹ It is possible that even in the absence of a clear genotype/phenotype association, knowledge that one has a genotype associated with increased risk of nicotine addiction or lung cancer may still affect individuals' behavior. Alternatively, even if there is a very strong relationship between a particular genetic variant and a clinical outcome, disclosure of the information may not influence behavior. For example, while the association between alpha-1-antitrypsin deficiency (ATD) and early onset emphysema in smokers is robust,³⁰ giving this information to children and their parents has not resulted in less smoking.

Newborn screening for ATD was conducted in Sweden between 1972-1974.³¹ However, this study was discontinued because of perceived psychological distress in parents.³² The impact of disclosing ATD on smoking behaviors of parents, and subsequently, on their children is unclear. Most of the studies have not shown a significant reduction in smoking in the parents or children, while demonstrating increased anxiety and distress.³³ Nevertheless, there have been proposals to screen pre-adolescents for ATD to prevent adolescent smoking.³⁴

There have been a few studies that have examined the impact of genetic information about smoking-related disease susceptibility on smoking behavior in

29. In addition to genes related to smoking behavior per se, other genes have been identified that are associated with smoking related morbidity, including the GSTM1 polymorphisms and lung cancer and the alpha 1 antitrypsin gene and emphysema. See generally Edyta Reszka & Wojciech Wasowicz, *Significance of Genetic Polymorphisms in Glutathione S-Transferase Multigene Family and Lung Cancer Risk*, 14 INT'L. J. OCCUP. MED. ENVTL. HEALTH 99 (2001); Christer Larsson, *Natural History and Life Expectancy in Severe Alpha₁ Antitrypsin Deficiency Pi Z*, 204 ACTA. MED. SCAND. 345 (1978).

30. See generally E. Piitulainen & T. Sveger, *Effect of Environmental and Clinical Factors on Lung Function and Respiratory Symptom in Adolescents with Alpha₁-Antitrypsin Deficiency*, 87 ACTA. PAEDIATRICALS 1120 (1998).

31. In this program, 200,000 infants were screened, and 184 of those infants were found to be at risk of developing early onset emphysema if they smoked or were exposed to smoke or other respiratory irritants. T. Thelin et al., *Identifying Children at High Somatic Risk: Parents' Long-Term Emotional Adjustment to Their Children's Alpha₁-Antitrypsin Deficiency*, 72 ACTA. PSYCHIATRY SCAND. 323, 323 (1985).

32. *Id.* at 328-329.

33. In a sub-cohort of 61 families, surveyed when the children were between the ages of 5-7, parents were just as likely to smoke as controls. See Thelin et al., *supra* note 10 at 1210. A subsequent follow-up assessment, when these subjects were between the ages of 18-20, indicated that adolescents with ATD were less likely to smoke (3 of 50 (6%)) compared to controls (8 of 48 (17%)). *Id.* at 1209. Two follow-up studies of 50 of these children, between 16 and 18 years of age, did not show any difference in the smoking rates of the adolescents or parents compared to controls. T. Sveger et al., *Lung Function in Adolescents with Alpha₁-Antitrypsin Deficiency*, 83 ACTA. PAEDIATRICALS 1170, 1173 (1994). See also, T. Sveger et al., *Clinical Features and Lung Function in 18-year-old Adolescents with Alpha₁-Antitrypsin Deficiency*, 84 ACTA. PAEDIATRICALS 815, 815-16 (1995). Further, in another report of a larger cohort of this ATD population, 13 of 128 (10%) currently smoked. See Piitulainen & T. Sveger, *supra* note 30 at 1123.

34. See generally Thelin et al., *supra* note 10.

adults. Lerman and colleagues conducted a randomized trial to assess the impact of feedback on genetic susceptibility to lung cancer related to the *CYP2D6* polymorphism.³⁵ Although the information produced positive changes in smoking-related beliefs and motivations, there were no significant differences in smoking quit rates after two or twelve months.³⁶ There was evidence for a small increase in depression symptoms that was not maintained at follow-up. In another randomized study, African-American smokers were recruited through a community clinic and offered a blood test for the *GST*³ gene (*GSTM1*) to determine susceptibility to tobacco-related cancers.³⁷ Eighty-three percent of the participants agreed to have a blood test for *GSTM1*.³⁸ At six months, smoking cessation was greater in participants offered the test (19% vs. 10%), but at twelve months the smoking cessation rates were comparable.³⁹

In contexts other than smoking, genetic information has been shown to limit impact on behavior in adolescents. While dietary interventions are effective in maintaining phenylalanine levels in an acceptable range to avoid neurocognitive effects in people with Phenylketonuria (PKU), adolescents do not always stay on the diet. In a recent study from the United Kingdom, approximately 70% of children younger than 10 years old were able to keep their phenylalanine levels in the acceptable range through diet range, but this decreased to approximately 20% for adolescents over the age of 15.⁴⁰ This illustrates the limitations of using personalized feedback about risk in adolescents to change their behavior in order to avoid adverse health consequences.

In light of the current data, there is a low likelihood of benefit to adolescents who participate in studies that involve the disclosure of participants' genotype for two reasons. First, there is a limited understanding of the genes associated with smoking related behaviors or the health consequences of smoking. Second, available data from other contexts suggests that relaying information about one's genetic risks rarely leads to significant behavioral change.

35. See generally Caryn Lerman et al., *Incorporating Biomarkers of Exposure and Genetic Susceptibility into Smoking Cessation Treatment: Effects on Smoking-Related Cognitions, Emotions, and Behavior Change*, 16 HEALTH PSYCHOLOGY 87 (1997).

36. *Id.*; see also Janet Audrain et al., *Genetic Susceptibility Testing in Smoking-Cessation Treatment: One- Year Outcomes of a Randomized Trial*, 22 ADDICT. BEHAV. 741, 741-42 (1997).

37. Colleen M. McBride et al., *Incorporating Genetic Susceptibility Feedback into a Smoking Cessation Program for African-American Smokers with Low Income*, 11 CANCER EPIDEMIOLOG. BIOMARKERS & PREV. 521, 522 (2002).

38. *Id.*

39. *Id.*

40. See J.H. Walter et al., *How Practical are Recommendations for Dietary Control in Phenylketonuria?*, 360 LANCET 55, 55 (2002).

B. Potential risks

While the issue of harm to individuals from disclosure of genetic information is not new, and has been previously addressed in several other contexts,⁴¹ what may be important in the case of genes associated with smoking behavior is the extent to which the conditions and behaviors involved are socially sensitive and engage notions of personal responsibility.⁴² Genes involved in dopamine and serotonin regulation, which have been a primary focus of research, have also been associated with risk for substance abuse more generally, including addiction to cocaine, addiction to alcohol use,⁴³ and a number of psychiatric conditions (e.g., Tourettes Syndrome,⁴⁴ Anxiety,⁴⁵ Attention Deficit Hyperactive Disorder (ADHD),⁴⁶ Post-traumatic Stress Disorder (PTSD),⁴⁷ Obsessive-Compulsive Disorder (OCD),⁴⁸ depression, and suicide⁴⁹). Genetic information relating to

41. See, e.g., Judith L. Benkendorf et al., *Patients' Attitudes About Autonomy and Confidentiality in Genetic Testing for Breast-Ovarian Cancer Susceptibility*, 73 AM. J. MED. GENE. 296 (1997); see also Jeffrey R. Botkin, *Protecting the Privacy of Family Members in Survey and Pedigree Research*, 285 JAMA 207 (2001); Gary N. McAbee & Jack Sherman, *Physician's Duty to Warn Third Parties About the Risk of Genetic Diseases*, 102 PEDIATRICS 140, 141-42 (1998).

42. Charles P. O'Brien & A. Thomas McLellan, *Myths About the Treatment of Addiction*, 347 LANCET 237, 237 (1996); see also A. Thomas McLellan et al., *Drug Dependence, a Chronic Medical Illness: Implications for Treatment, Insurance, and Outcomes Evaluation*, 284 JAMA 1689, 1690 (2000).

43. See, e.g., Kenneth Blum et al., *Allelic Association of Human Dopamine D₂ Receptor Gene in Alcoholism*, 263 JAMA 2055 (1990); Noble, *supra* note 13; Comings et al., *supra* note 13; Dirk Lichtermann et al., *Support for Allelic Association of a Polymorphic Site in the Promoter Region of the Serotonin Transporter Gene with Risk for Alcohol Dependence*, 157 AM. J. PSYCHIATRY 2045 (2000); Matsushita et al., *supra* note 13.

44. D.E. Comings et al., *Studies of the Potential Role of the Dopamine D₁ Receptor Gene in Addictive Behaviors*, 2 MOLECULAR PSYCHIATRY 44, 44 (1997) (citing Kenneth Blum et al., *Dopamine D₂ Receptor Gene Radiants: Association and Linkage Studies in Impulsive, Addictive and Compulsive Disorders*, 5 PHARMACOGENETICS 121 (1995)).

45. See generally Klaus-Peter Lesch et al., *Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region*, 274 SCI. 1527 (1996).

46. D.E. Comings et al., *Dopamine D₂ Receptor (DRD2) Gene and Susceptibility to Posttraumatic Stress Disorder: A Study and Replication*, 40 BIO. PSYCHIATRY 368, 368 (1996) (citing D. E. Comings et al., *The Dopamine D₂ Receptor Locus as a Modifying Gene in Neuropsychiatric Disorders*, 266 JAMA 1793 (1991)); see also Pierandrea Muglia et al., *Adult Attention Deficit Hyperactivity Disorder and the Dopamine D4 Receptor Gene*, 96 AM. J. MED. GENE 273, 274 (2000).

47. See Comings et al., *supra* note 44 at 368.

48. David C. Rowe et al., *The Relation of the Dopamine Transporter Gene (DAT1) to Symptoms of Internalizing Disorders in Children*, 28 BEHAV. GENE. 215, 215 (1998).

49. David A. Nielson et al., *A Tryptophan Hydroxylase Gene Marker for Suicidality and Alcoholism*, 55 ARCH. GEN. PSYCHIATRY 593, 593-95 (1998); see Frank Bellivier et al., *Serotonin Transporter Gene Polymorphisms in Patients with Unipolar or Bipolar Depression*, 255 NEUROSCIENCE LETTERS 143, 143 (1998) (citing A.D. Ogilvie et al., *Polymorphism in Serotonin Transporter Gene Associated with Susceptibility to Major Depression*, 347 LANCET 731 (1996)).

behaviors such as substance abuse and psychiatric disorders may be far more stigmatizing to individuals relative to stigma associated with smoking.⁵⁰

The range of pleiotropic associations of smoking-related genes may also lead to greater risk of discrimination in future employment or health insurance contexts.⁵¹ Current smokers already face significant problems with insurance, employment, and social stigmatization.⁵² This group might be particularly vulnerable to further discrimination.⁵³ However, because smokers already face substantial social discrimination, additional problems related to genetic information may not be so significant. It is possible too that some might view genetic information as a mitigating factor to explain smokers' addiction to nicotine. However, because these pleiotropic associations are tentative, and the role of these genes in the behavior of addiction is not clear, it will be difficult to estimate the likelihood and magnitude of the potential harms related with such associations. While the meaning of these identified genotype-phenotype relationships have yet to be fully understood, it seems likely that there would be additional risks for participants in studies that provide information about genotypes with potentially stigmatizing pleiotropic associations in contrast to studies that provide information about risk for health consequences of smoking that do not also have additional genetic associations.

There may be specific risks of involving adolescents in research that discloses genetic risks related to smoking. "Labeling" adolescents, as being at risk for addiction or at risk for health complications of smoking, may be particularly damaging to their self-image and their view of their ability to shape their future.⁵⁴ There may also be an adverse impact of this information on smoking behavior *per*

50. See generally M.R.B. Davies, *The Stigma of Anxiety Disorders*, 54 INT'L. J. CLIN. PRAC. 44 (2000); Bruce G. Link et al., *On Stigma and Its Consequences: Evidence from a Longitudinal Study of Men with Dual Diagnoses of Mental Illness and Substance Abuse*, 38 J. HEALTH & SOC. BEHAV. 177 (1997) [hereinafter Bruce G. Link et al. *On Stigma*]; Bruce G. Link et al., *Public Conceptions of Mental Illness: Labels, Causes, Dangerousness, and Social Distance*, 89 AM. J. PUB. HEALTH 1328 (1999) [hereinafter Bruce G. Link et al. *Public Conceptions*]; Jo C. Phelan et al., *Psychiatric Illness and Family Stigma*, 24 SCHIZOPHRENIA BULL. 115 (1998); E.B. Ritson, *Alcohol, Drugs and Stigma*, 53 INT'L. J. CLIN. PRAC. 549 (1999).

51. See generally Kathy L. Hudson et al., *Genetics Discrimination and Health Insurance: An Urgent Need for Reform*, 270 SCI. 391 (1995).

52. See generally Scott Burris, *Disease Stigma in U.S. Public Health Law*, 30 J. L. MED. & ETHICS 179 (2002).

53. It is unknown to what extent additional pleiotropic associations of smoking-related genes might exacerbate the potential for discrimination against individuals identified having particular risk-conferring alleles. For example, one could imagine that self-insured employers might more likely discriminate against such persons based on a higher health care costs associated with substance abuse and mental health. See generally Deborah W. Garnick et al., *Do Individuals with Substance Abuse Diagnoses Incur Higher Charges than Individuals with Other Chronic Conditions?*, 14 J. OF SUBSTANCE ABUSE TREATMENT 457 (1997).

54. See Skinner et al., D. Cohn et al., and Murray, *supra* note 19.

se due to confusion about the meaning of genetic information. Adolescents who are told that they have a genotype associated with a reduced likelihood of an adverse health outcome from smoking might be resistant to public health messages about the risks of smoking and more willing to smoke. Adolescents who are told that they do not have a particular genotype associated with an increased risk of nicotine addiction, for example, may erroneously believe that they can smoke without developing a habit. Adolescents who already smoke who are told that they possess a genotype associated with increased risk of nicotine addiction might conclude that it is not worth trying to quit. Thus, providing genetic information to adolescents to positively motivate behavior might turn out to have adverse psychological effects, and might even inadvertently promote smoking behavior.

C. *Balancing Benefits and Risks*

In research involving children, federal regulations require that the “prospect of direct benefit” must justify the risks.⁵⁵ Such risk/benefit assessments are inherently subjective but critical, nonetheless. One operational use of this assessment is in choosing between alternative study designs. The evaluation of risks and benefits can be done comparatively. Given a specific amount of risk posed by a particular study, for example, one should choose the design with the greatest benefits to participants. Similarly, if the anticipated benefits to participants are fixed, one should select the design that poses the least risk to study participants. This approach can be useful in deciding which studies to conduct *initially*, and may be particularly relevant to initial studies about the impact of genetic information on smoking behavior, since there is great uncertainty about the likelihood of risks and potential benefits.

There may be a more favorable risk/benefit ratio for studies that target smokers than nonsmokers. The potential direct *benefits* to smokers are arguably greater (even though the public health benefit of prevention is more profound) since they are currently engaged in a behavior with substantial health risks.

Additionally, the *harms* may be more significant in studies that use genetic information to prevent smoking than studies that would use such information to facilitate quitting. First the potential population for preventive interventions is much larger (i.e., all at risk individuals), so the impact of any risks would create a greater public health concern. Further, while risks of stigmatization might occur in both smokers and nonsmokers, the concerns about discrimination may be less salient for smokers who already face significant discrimination.

Given that, comparatively speaking, the risks are lower to smokers and to adults, we argue that the first studies in which genetic status is communicated to participants should be conducted with adult smokers recruited into treatment trials. Such studies will provide important data on the impact of genetic information on

55. 45 C.F.R. §46.405 (2001).

smoking behavior, the possibility of achieving improved quit rates through genetically tailored treatments, and the possible unintended adverse effects associated with this genetic information among adults. Only after such studies have provided greater clarity about anticipated benefits and risks experienced by adult smokers would we support the initiation of prevention trials. Initial prevention studies should be conducted in young adults between the ages of 18-25, recruited through community or college-based programs. Members of this age group are old enough to make their own decisions, but young enough to still be at risk to begin smoking. Only once such studies are completed with an acceptable risk/benefit profile, should prevention studies be conducted in minors. Even then, prevention trials in minors should initially focus on assessing genes associated with health-related consequences of smoking (e.g. alpha-1-antitrypsin), before assessing genes associated with smoking behavior since the former may have fewer risks than the latter.

III. THREATS TO INFORMED AND VOLUNTARY DECISION-MAKING

In addition to concerns about the benefits and risks of enrolling adolescents in research that provides genetic information, there are concerns about their ability to engage in a valid and meaningful informed consent process. There are two main threats to the ability of adolescents to engage in informed and voluntary decision-making. Although both of these concerns apply when adolescents are enrolled in any kind of research, there are some unique aspects of these concerns in the specific case of behavioral genetics intervention trials.

First, there may be general worries that adolescents may not have the ability to appreciate the risks of the research and may be more vulnerable to undue influences to enroll in research. There have been several empirical studies that have focused on the impact of developmental changes on decision-making⁵⁶ and the effect variation in psychological states may have on children's ability to assess risks associated with research participation.⁵⁷ Evidence suggests that most children younger than 9-years-old cannot be expected to consent or assent to clinical research in a meaningful way.⁵⁸ However, most adolescents, at least past the ages of 14 or 15, are able to function as well as adult research participants under most circumstances.⁵⁹ Based on this evidence alone, one can argue that it is morally

56. See Skinner et al., Cohn et al., and Murray *supra* note 19.

57. See, e.g., Lorah D. Dorn et al., *Informed Consent in Children and Adolescents: Age, Maturation and Psychological State*, 16 J. ADOLESC. HEALTH 185 (1995).

58. Nancy Ondrusek et al., *Empirical Examination of the Ability of Children to Consent to Clinical Research*, 24 J. MED. ETHICS 158, 158 (1998).

59. Society for Adolescent Medicine, *Guidelines for Adolescent Health Research*, 17 J. ADOLESC. HEALTH 270, 272 (1995); see also Anne C. Petersen & Nancy Leffert, *Developmental Issues Influencing Guidelines for Adolescent Health Research: A Review*, 17 J. ADOLESC. HEALTH 298, 299 (1995).

justifiable to include adolescents in clinical research that assesses the impact of genetic information on smoking behavior. However, this evidence is derived from studies that have been limited to populations of *unhealthy* children who were participants in clinical/therapeutic research⁶⁰ or psychosocial research.⁶¹ Less is known about how healthy children, who may be at increased risk for inherited susceptibility to nicotine addiction or the health consequences of smoking, will assess benefits and risks. Further research is needed in this area in order to guide decisions of Institutional Review Boards and others evaluating genetic susceptibility studies of healthy children.

A second concern is the degree to which adolescents will be subjected to undue influences from parents, the researchers, or other social contacts, including friends, teachers or health care practitioners. This is particularly true when research may offer a prospect of direct benefit, parents may be more inclined to pressure adolescents to participate. It is imperative to give careful consideration to the circumstances under which adolescents would be recruited for research on genetics and smoking. Although evidence suggests that adolescents are more likely to be involved in informed consent discussions than younger children, and their opinions are given more weight because of greater cognitive and emotional capacity,⁶² they are still highly impressionable. The potential for undue influence by others is a risk in any research involving minors. However, the degree to which there is an added risk in behavioral genetics research turns on whether genetic test results will be disclosed to the participants as part of the research.

The recruitment experience in a longitudinal cohort study to evaluate the genetic, psychological and social contributions to adolescent smoking⁶³ did not suggest that participants were unduly influenced to enroll. In this study, adolescents were recruited after first getting parental permission and only 54% of parents gave their permission. Lack of interest in the goals of the project was the most commonly cited reason for parents declining (47%).⁶⁴ Parents were almost

60. Gail Geller et al., *Informed Consent for Enrolling Minors in Genetic Susceptibility Research: A Qualitative Study of At-Risk Children's and Parents' Views about the Role Children Should Play in Decision-Making*, J. ADOLES. HEALTH (in press) (citing generally Susan Michie et al., *Predictive Genetic Testing in Children and Adults: A Study of Emotional Impact*, 38 J. MED. GENE. 519 (2001); Marion Broome et al., *Children in Research: The Experience of Ill Children and Adolescents*, 7 J. FAM. NURS. 32, 32-33 (2001); E.J. Susman et al., *Participation in Biomedical Research: The Consent Process as Viewed by Children, Adolescents, Young Adults, and Physicians*, 121 J. PEDS. 547 (1992); Marion E. Broome, *Consent (Assent) for Research with Pediatric Patients*, 15 SEMINARS IN ONC. NURS. 96 (1999)).

61. *Id.* (citing generally Sue Miller, *Researching Children: Issues Arising from a Phenomenological Study with Children Who Have Diabetes Mellitus*, 31 J. ADV. NURS. 1228 (2000); Michael Rich et al., *Video Intervention/Prevention Assessment: A Patient-Centered Methodology for Understanding the Adolescent Illness Experience*, 27 J. ADOLESC. HEALTH 155 (2000)).

62. *Id.* at 19-20.

63. See generally Audrain et al., *supra* note 9.

64. Audrian et al., *supra* note 9 at 251-52. Concerns about confidentiality were expressed by 16% of declining parents. Almost half of these parents raised specific concerns about genetics, and the rest

three times more likely to attribute this lack of interest to the adolescents rather than to themselves.⁶⁵ This suggests that family members discussed the project with one another prior to making their decision and that parents generally respected the decisions of their teenagers regarding participation. However, genetic test results were not disclosed as part of this study.

Other studies also have demonstrated the tendency of parents to defer to their adolescent children regarding decisions about participation in “nontherapeutic” research. However, in studies that offer potential benefit to teenage participants, parents are more likely to encourage their children to participate (or override their children’s refusal).⁶⁶ Studies that offer the results of genetic testing and/or the opportunity to participate in a preventive intervention might be perceived by parents as having potential benefits for their adolescents.⁶⁷ Moreover, genetic information about adolescents has potential relevance for the parents themselves. To the degree that parents derive some personal benefit from learning about their own susceptibility to nicotine addiction or to adverse health consequences of smoking, and perceive a potential benefit to enrolling their adolescents in prevention or treatment trials, they might be more likely to “coerce” their adolescents into participating in such research.⁶⁸ Because of concern about undue influences on adolescent decision-making, particularly when the benefits do not justify the potential risks, we believe that minors should be excluded from initial studies.

IV. CONCLUSION

Clinical studies that use genetic information to influence smoking behavior among adolescents are seductive because they may lead to important new tools to address a seemingly intractable public health problem. However, because of an uncertain and potentially less favorable risk/benefit ratio and limitations of adolescent authority to make informed and voluntary decisions, initial studies that use genetic information to influence smoking behavior should not target adolescents.⁶⁹ Only once there is additional information about the empirical

reflected nonspecific concerns over data privacy. Confidentiality regarding adolescent genetic testing was less of a concern, perhaps because this study did not provide the adolescents with their genetic test results.

65. Audrian et al., *supra* note 9 at 252.

66. See generally Gail Geller et al., *Mothers and Daughters from Breast Cancer Families: A Qualitative Study of their Perceptions of the Risks and Benefits Associated with Minors’ Participation in Genetic Susceptibility Research*, 55 JAMWA 280 (2000); Barbara A. Bernhardt et al., *Parents’ and Children’s Attitudes Toward the Enrollment of Minors in Genetic Susceptibility Research: Implications for Informed Consent*, 2002 AM. J. MED. GENETICS DRAFT 1 (in press).

67. Geller et al., *supra* note 66 at 282, 283; Bernhardt et al., *supra* note 66 at 17-20.

68. Bernhardt et al., *supra* note 66 at 22.

69. Table 1 provides a graphical representation of the phased-in approach proposed in this article. See *supra* note 14 and accompanying text.

benefits and risks of providing such information in the context of treatment trials for adult smokers should prevention studies be conducted. These prevention trials should first be conducted in young adults between the age of 18 and 25 before enrolling minor adolescents. Additionally, prevention trials in adolescents should

Tbl 1: Phased-in Approach to Research on Genetics & Smoking-Related Behaviors

Type of Research (population)	Age of Target Population	Phase 1	Phase 2	Phase 3
Treatment Trials (smokers)	Adults (≥ 18)	<input checked="" type="checkbox"/>		
Prevention Trials (nonsmokers)	Young Adults (18-25)		<input checked="" type="checkbox"/>	
	Minors (10-17)			<input checked="" type="checkbox"/>

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first provide information related to the health consequences of smoking compared to studies that provide information about smoking related behaviors.

While we acknowledge that this “phased-in” approach will slow down the integration of clinical approaches based on genetic information, we believe such caution is warranted. Until there is sufficient evidence that genetic-based smoking prevention and treatment interventions can play an important role in improving public health among adults, there is no justification for exposing adolescent participants to unnecessary risks.