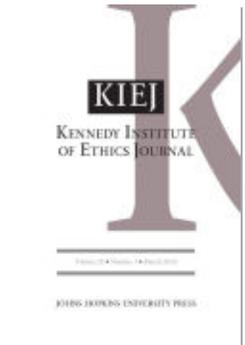# Ethical Guidelines for Genetic Research on Alcohol Addiction and Its Applications

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Ethical Guidelines for Genetic Research on Alcohol Addiction and Its Applications

ABSTRACT. Research on the genomic correlates to addiction raises ethical issues in a number of different domains. In this paper, we evaluate the status of genetic research on alcohol dependence as background to addressing the ethical issues raised in conducting research on addiction and the application of that research to the formulation of public policies. We conclude that genetic testing is not yet ready for use in the prediction of alcohol dependence liability. Pharmacogenetic testing for responses to treatments may have more clinical utility, although additional research is required to demonstrate utility and cost-effectiveness. Genetic research on addiction raises potential risks for participants that must be clearly communicated to participants, including limitations on the ability of researchers to protect their privacy. Responsible communication of research findings is essential to prevent common misunderstandings about the role of genetics in addiction liability, to prevent its premature or inappropriate use, and to reduce discrimination and stigmatization experienced by addicted individuals. More research is needed to determine the impact of genetic explanations on addicted individuals, treatment-seeking behavior, and on public attitudes towards addicted persons. Importantly, genetic research on addiction must not be at the expense of investments in social, behavioral, and psychological research on addiction.

INTRODUCTION

The misuse of alcohol inflicts a major toll on individual users, their families, and the wider society. This includes disruptions of family life, violence, absenteeism and problems in the workplace, child neglect and abuse, and excess morbidity and mortality (World Health Organization 2011, 24). The World Health Organization (WHO) estimates that alcohol ranks eighth among global risk factors for death and is the third leading global risk factor for disease and disability (World Health

Organization 2011, 34). In the United States, alcohol dependence affects four to five percent of the population at any given time (Foroud, Edenberg, and Crabbe 2010, 64). Alcohol dependence also exacts a significant financial toll. The Centers for Disease Control and Prevention estimates that the cost of alcohol disorders in the United States reached $249 billion in 2010 (Sacks et al. 2015).

The increasing evidence that addiction to alcohol has a genetic contribution from studies of families has given rise to research to improve our biological understanding of addiction and thereby our ability to more effectively treat those afflicted and possibly prevent addictive disorders. Advancements arising from the mapping of the human genome and the application of high-throughput sequencing have reduced the costs of genome wide scans and heralded optimistic predictions about the potential use of genetic information to personalize medicine and improve health (Auffray et al. 2016; Collins et al. 2003). Proponents of personalized genomic medicine have proposed that genetic research be used preventively to identify healthy persons at a greater risk of developing alcohol dependence so as to be able to intervene (Yan et al. 2014). Others have suggested that genetic technology could be used therapeutically to allow clinicians to better match drug-dependent persons to more effective treatments—an approach termed *pharmacogenetics* (Sturgess et al. 2011). Given the significant challenges in effectively treating persons with alcohol dependence and in reducing harmful alcohol consumption, such proposals have considerable appeal. Substantial investments have been made in genetic research related to potential addiction management.

However, like other areas of genetics and particularly behavioral genetics, genetic research on addiction raises ethical issues related both to the way the research is conducted and how the findings are interpreted and used. Genetic research on addiction touches on sensitive questions about the determinants of human behavior, the balance between freedom and determinism, and the extent to which we share our genetic identity with other members of our family and our broader social community. Research involving addicted participants, who may be cognitively, psychologically, or socially impaired, requires special safeguards. In addition, advances in genetics and the development of large databases and biobanks to study associations between genetic or genomic variation and diseases have made the protection of privacy and confidentiality of genetic data far more difficult. While research identifying genes predictive of addiction liability and treatment response has the potential to improve public health, it may

also be misused or misinterpreted in ways that harm the individual and society more broadly. For example, it may negatively influence community attitudes to persons with a genetic predisposition to addiction, causing additional stigmatization of such individuals (Berghmans et al. 2009).

This article considers ethical issues raised by genetic research on alcohol dependence and identifies ways to minimize its potentially deleterious effects. In doing so, the article examines recent developments in genetic research on alcohol dependence, including genome-wide association studies that have significant implications for the treatment of alcohol dependence. Previous studies have appraised ethical issues related to genetic research in mental illness more generally, but alcohol dependence raises unique issues that need to be assessed specifically. In contrast with previous reviews that have looked at single issues, we have also tried to address the ethical issues raised in both research and treatment more comprehensively. The paper was informed by a multi-year project that brought together leading multidisciplinary researchers to examine these issues, which resulted in an edited volume (Chapman 2012) and a subsequent consensus workshop. However, the views expressed here are our own.

The article has five sections. The first section provides a brief overview of the status of the science and its implications for potential clinical application of genetic technologies for addiction. The second section focuses on the ethical issues raised in conducting research on alcohol-dependent subjects and the third on using children of alcohol-dependent parents as research subjects. The fourth section addresses privacy concerns, and the fifth communication issues.

I. BRIEF OVERVIEW OF THE STATUS OF GENETIC RESEARCH AND POTENTIAL APPLICATIONS FOR ALCOHOL DEPENDENCE

Family, adoption, and twin studies have provided convergent evidence that heredity plays a major role in alcohol dependence. Genetic factors are estimated to be associated with 50 to 60 percent of the total variance in risk of developing alcoholism (Foroud, Edenberg, and Crabbe 2010; Verhulst, Neale, and Kendler 2015). Advances utilizing next-generation sequencing technologies and methodologies such as linkage, association, and genome-wide association studies have made it possible to identify a number of genetic variants thought to be involved in the development and persistence of alcohol dependence. Most of these genetic variants encode alcohol-metabolizing enzymes and neurotransmitter receptors (Edenberg and Foroud 2013; Foroud, Edenberg, and Crabbe 2010; Mathews, Carter, and Hall 2012, 18–21).

Despite a considerable research investment, the feasibility of using predictive screening, particularly at a population level, to identify individuals more susceptible to alcohol dependence remains elusive. Research has not been able to discover commonly occurring susceptibility alleles that strongly predict addiction risk. Candidate alleles (variant forms of a gene) identified so far have at most a modest effect. This means that a given allele found to be associated with alcohol dependence increases the risk only incrementally. A family history of alcoholism still offers more predictive value than the gene variants discovered to date (Mathews, Carter, and Hall 2012; Foroud, Edenberg, and Crabbe 2010).

A further complication is that predisposition toward alcohol dependence is a complex disorder shaped by multiple alleles, each contributing a small effect, that dynamically interact with each other and with environmental factors. Recent research has identified a network of genes that appear to work together in determining a predisposition to alcoholism (Farris et al. 2015). Disease liability can also be affected by epigenetic (environmental and social) modifications that alter gene expression without changing the gene's DNA sequence (Foroud, Edenberg, and Crabbe 2010; Krishnan et al. 2014). The multiplicity of genes involved and the complexity of unraveling the genetic contributions to alcohol dependence make it unlikely that genetic research will be able to contribute to predictive genetic screening to identify individuals disposed to addictive disorders in the near future.

Moreover, the large number of genes involved means that population screening for alcohol dependence would be prohibitively expensive. Given the small effect sizes for susceptibility alleles, extremely high numbers of people would need to be screened to detect one "high-risk" case. Also, most people will likely be found to have "modest" risk. Triaging screening on the basis of family history of alcohol dependence, and thus reducing the number of people tested, would be a less expensive proposition. However, the costs of screening even this smaller more select group could be justified only if the addition of genetic information improved upon predictions based on family history. It is unclear as yet if it does (Mathews, Carter, and Hall 2012, 23–24).

Pharmacogenetic research on addiction seems more promising and more likely to benefit public health in the near future. Pharmacogenetic testing has the capacity to help clinicians to select the treatment and determine the dose of treatment that will yield the best outcomes in an individual while minimizing side effects and relapse. For a pharmacogenetic test to be clinically useful, though, the genes tested need to be highly prevalent

and predictive of a differential treatment response. With respect to treatment for alcohol dependence, the Asp40 allele of the OPRM1 gene for response to naltrexone treatment best meets the aforementioned criteria, at least in Asian and Caucasian Americans. Asp40 is found in 48 percent of Americans of Asian descent and 15 to 18 percent of Caucasian Americans, but less than 5 percent of African–Americans (Kuehn 2009). Those possessing it are three times more likely to respond to naltrexone therapy for alcohol dependence than those homozygous for the Asn40 allele (Anton et al. 2006; Oslin et al. 2003; Ray and Hutchison 2007). Cost-effectiveness analyses are needed to determine whether using this test provides a sufficient gain in treatment outcome to justify the costs of its use in the whole population as there is a lower prevalence of this variant in Caucasian and African–Americans than in those of Asian descent. If the test does prove to be cost-effective and acceptable to both clinicians and patients, it will provide a good model of how a pharmacogenetic test can be used in the addictions field.

II. CONDUCTING RESEARCH WITH ALCOHOL-DEPENDENT SUBJECTS

Because substance use disorders are so highly stigmatizing, genetic research related to alcohol addiction has significant implications for the individual research participant (Pescosolido et al. 2010). Subjects in a study of the genetics of alcohol dependence have the risk or experiencing stigma, discrimination, or loss of opportunities just from being identified as participants.

There are conflicting views as to whether genetic explanations of addiction increase or decrease stigmatization (Buchman and Reiner 2009). Some believe that geneticization will reduce stigmatization and discrimination of persons with addiction because they are not viewed as having become addicted through moral weakness or of their own volition (DeCamp and Sugarman 2004a; 2004b; 2004c). Another view is that genetic explanations increase stigma and discrimination because the genes that predispose addiction are viewed as an unchangeable characteristic of the person (Berghmans et al. 2009). Research on the genetic basis of other psychiatric disorders suggests biological explanations may in fact harden people's attitudes, increasing stigmatization and social distance (Buchman and Reiner 2009; Read and Harré 2001). Additionally, it has been suggested that adopting a neurobiological view of addiction may result in far-reaching consequences for stigma and the identity of addicted individuals in those people with addictions deemed to be neurobiologically

abnormal and incurable (Buchman and Reiner 2009). More research is needed to determine which of these outcomes is more likely.

Like other forms of genetic research, genetic research on addiction expands the ambit of risks and potential harms from the individual participant to family members who potentially share their generic heritage. Family members may also suffer from the social stigma and psychological burden of knowing they or other family members are at a genetically increased risk of addiction. Recruitment procedures for children may lead to inadvertent disclosure of familial risk. If ethnic and racial groups or other communities with different allele frequencies associated with addictive behaviors are discovered, this will increase the risk of discrimination and stigmatization of those populations.

Therefore it seems appropriate for alcohol-dependent persons to be treated as a potentially vulnerable population when they are recruited as research subjects. Substance abusers have been shown to have impaired attention, cognition, and retention of important information as a result of acute intoxication or withdrawal (Festinger and Dugosh 2012, 45). However, that does not mean that they are incapable of giving meaningful informed consent. Autonomy in all areas of life is not automatically undermined by addiction. While empirical research on addicted individuals and the consent process is limited, it has not found evidence that this population suffers from impairment in decision-making related to giving informed consent (Carter and Hall 2008). Nevertheless, it is important to assess potential candidates individually on their ability to provide meaningful informed consent. Assessment of the ability to provide meaningful informed consent should exclude those who are intoxicated and experiencing withdrawal, using appropriate scales (Carter and Hall 2008).

There are other reasons for caution when dealing with substance dependent candidates, such as their generally lower levels of educational attainment and lower socio-economic status, the health issues and psychological effects associated with addiction, and the co-morbidities that many of them suffer (Festinger and Dugosh 2012). Also many substance abusers have life situations that may affect the autonomy of their decisions to participate. For example, researchers often recruit substance abusers from settings that are implicitly "coercive" such as inpatient units, detoxification facilities, and prisons. Criminal justice clients may perceive, correctly or incorrectly, that participation in research studies may affect their sentence and their access to treatment (Festinger and Dugosh 2012).

As in other research studies, a meaningful informed consent process is a fundamental ethical requirement. It is essential to ensure that participants, particularly vulnerable subjects, understand the nature of the research, their rights, and to what they are consenting. The informed consent process must make clear both the individual and social risks and benefits of participating in the research as well as the right to refuse to participate and/or to withdrawal from participation in a manner understandable to this population. It is also important to clarify that participating in the research is not a precondition for clinical treatment. Nor is it a substitute. Further, researchers also need to provide participants with information on the potential findings, what kind of incidental findings might occur, and which kinds of findings will be communicated to them. For example, participants should be informed about whether they will receive individualized information or just the aggregate research results. In most cases the individual research results will not be clinically meaningful and are therefore inappropriate to share with participants and this should be explained. Interested participants should be given the opportunity to receive summaries of general research findings. In addition, researchers should have a plan in place with lists of contacts if something of clear clinical importance is discovered during the research, such as medical (including psychological) conditions. The consent form should indicate that if something of clinical importance is found, participants will be informed and given information on potential places to go for assistance. Potential research subjects also need to be informed about the specific measures that will be used to protect their privacy and the likely effectiveness of each of them as part of the informed consent process as input to their assessing the risks and benefits of participating in the research. (For more on these measures and their expected effectiveness see Section IV.)

Conducting the informed consent procedure may be of little use without adequate validation to determine whether potential research participants heard, understood, and can recall what they were told. Options for increasing understanding and retention of the components of informed consent include simplifying the structure and content of consent materials to improve readability, using audio–visual technologies such as multimedia, interactive, and web-based technologies, and appointing an independent third party or "research intermediary" to interpret the document and advocate on behalf of the research subject. A corrected feedback process to assess an individual's knowledge and comprehension of the informed consent information following the initial review of the consent form and

then provide participants with corrected feedback about their incorrect items is another intervention associated with improvements both in initial comprehension and in longer-term retention of informed consent information. More research is necessary to evaluate the effectiveness of these options when working with alcohol-dependent subjects (Festinger and Dugosh 2012).

Concerns have been raised about the issue of remuneration for research participants who have substance use disorders—both whether cash incentives will impose an undue influence and the possibility that the cash will be used to purchase more alcohol or drugs. The low levels of educational attainment, high rates of unemployment, low income levels, and generally lower socio-economic status that are characteristic of many substance abusers can make them more susceptible to monetary influence (Festinger and Dugosh 2012). Nevertheless, addicted individuals should be compensated for their expenses, time, and participation, as would any other individual. Their motivation for participating in research is no different from the general population (Fry and Dwyer 2001), and they should not be discriminated against simply as a result of their addiction, although payments should not be so large as to unduly influence addicted individuals. There is currently no evidence that reasonable compensation increases use of drugs and alcohol (Festinger et al. 2005). To reduce the possibility that cash payments could be used to purchase alcohol or drugs, it may be preferable to compensate participants with gift cards and other non-monetary items or services (Fisher, Hasin, and Appelbaum 2012).

III. CONDUCTING RESEARCH ON CHILDREN FROM HIGH-RISK FAMILIES

Enrolling children from high-risk families in research studies of the genetics of addictive disorders poses a number of significant and unique ethical challenges. These include recruitment, obtaining consent or assent from the children, and potential exploitation by researchers and/or parents who may themselves be addicted (McMahon 2012). Arguably, researchers have a much heightened obligation to protect minors participating in genetic research because children do not typically have the legal authority to make informed decisions on their own. There is also the risk that children will be pressured by their families to participate because of the benefits accruing to other members. Additionally, children may have particular difficulty understanding the right of refusal. Research with minor asymptomatic children of addicted parents may also increase the risk that they will be perceived by themselves and others as at risk for

addiction or as particularly problematic in other ways (McMahon 2012). There is also the possibility that research may expose the children and/or their families to the danger of disclosing illicit or criminal activities (see e.g., Williamson et al. 2005).

While it is necessary to obtain consent from a legally authorized representative, such as a guardian or close family member, before enrolling children in an addiction study, children should participate in the informed consent process as fully as is possible, given their age and cognitive development. Children may not be able legally to provide informed consent, but it is important to secure their assent to participation in the research. Where there is a risk of reidentification, research should be limited to children who are able to understand and meaningfully consent to the research.

Where there is no risk of reidentification, the child's assent and parent/guardian consent may be sufficient. Consent for blanket reuse of stored data and biological samples from children should never be solicited. Indeed, Cargill argues forcefully that the very nature of biobanking makes true informed consent an impossible goal, as unforeseen (and perhaps unforeseeable) future research projects and risks undermine the possibility of consent being well-informed (Cargill 2016). Insofar as one accepts those arguments, additional caution will be required for participants who are not of an age to understand the open-ended risks they are accepting by permitting the biobanking of materials; further, the longer samples are stored, the greater the challenge of potential unforeseen risks arising with uses that could not have been anticipated when the samples were taken (Cargill 2016). If children's genetic information or samples are stored in a biobank for potential reuse, they should be reconsented at adulthood. If consent is not provided, the samples or information should be destroyed (Resnick 2012).

Because children with a substance-abusing parent are at greater risk for child abuse and neglect, as well as clinically significant emotional and behavioral difficulties, researchers must have clear procedures for responding to issues related to the well-being of the children. It is important to inform parents of situations in which the researchers will be required to violate confidentiality, for example, the existence of mandatory reporting of child abuse or neglect, and procedures need to be in place to do so.

Selection of children should be representative of the sample population. Children in state care should not be excluded from research; nor should

they be deliberately targeted because of the ease of recruitment. Because of the greater risks of exploitation, additional safeguards may be needed when recruiting children in the custody of the child welfare system, such as appointing an advocate who is independent of the researchers and the guardian organization to ensure that the study is not unusually risky for or otherwise against the interests of an individual child (Brock 2013; Varma and Wendler 2008).

It is unacceptable to use incentive payments to parents to encourage the participation of their children because of the risk that children may be coerced to participate. Additional payments to participants in research for the inclusion of children should also be discouraged. Payment may be made to offset expenses incurred or believed likely to be incurred through the children's participation. Meaningful age appropriate compensation for children should be provided, such as toys or books.

IV. PROTECTING THE PRIVACY AND CONFIDENTIALITY OF DATA

Researchers have an ethical and legal responsibility to protect the privacy and confidentiality of research data. This obligation is particularly important when conducting genetic research on alcohol dependence because of the potentially harmful consequences to the subjects from others accessing the genetic information. Therefore researchers have a responsibility to attempt to minimize the risk of disclosure. However, protecting the privacy and confidentiality of genetic data in an era of electronic health records and genetic databases poses numerous challenges.

Current U.S. regulations rely on deidentification to protect the privacy and confidentiality of research subjects, but deidentification alone is inadequate to fully protect genetic privacy (Rothstein 2012, 90). Individuals can be identified from a deidentified genomic database with access to 30 to 80 statistically independent single nucleotide polymorphisms (McGuire and Gibbs 2006). It is also possible to reidentify deidentified health records by matching phenotypes associated with the DNA to identified phenotypes from other databases with genomic information or from matching health records with computerized network databases containing voter registration records and other publicly available sources. Coded deidentification alone is not adequate to protect privacy. Full anonymization (at the point of collection) is better, but given how little data are necessary to uniquely identify individuals, it will rarely be sufficient to protect privacy and confidentiality.

One option to protect sensitive genetic data from legal subpoena is to seek a certificate of confidentiality from the National Institutes of Health (NIH) to protect research data from third-party requests. Certificates of Confidentiality are issued by NIH to protect investigators and institutions from being compelled to release information in a civil, criminal, administrative, legislative, or other proceeding that would identify research participants (Lazzarini 2012, 98). It has been suggested that because institutional review boards (IRBs) have an obligation to protect the privacy of research subjects and the confidentiality of data that are collected that IRBs should require certificates in some cases (Lazzarini 2012, 99). However, it is unclear as to whether certificates can withstand all legal challenges (Lazzarini 2012, 101–02).

Genomic biobanks that contain biological samples and databases in which digitized information about genes, genetic markers, common genetic variants, or whole genomes is deposited play an increasing role in addiction research. The databases make it possible for researchers to study thousands of genes or entire genomes in large populations to identify genetic variants related to alcohol dependence. While genomic databases are an important tool in genomic research, it is impossible to guarantee absolute privacy for genetic information when the biological samples are banked or large amounts of genomic or other data are stored. This is importantly different from research in which information and samples are used once before being destroyed, with the resulting data fully anonymized. The risks to individuals whose samples or information are stored in biobank repositories will depend on whether the information is identified or deidentified; whether informed consent was obtained (if indeed meaningful informed consent is possible in this context, see Cargill 2016), and if so whether it was limited or general; whether the research is on a sensitive topic; and what kinds of oversight exist (Rothstein 2012). In many circumstances individuals were not informed that the samples they sent for testing or the tissue resulting from surgical procedures would be retained for research. In other cases, researchers relied on a "presumed consent" process: data are incorporated unless individuals—who may not be aware of the procedure—opt out in writing. A preferable approach would be to use an explicit opt-in procedure that respects informed consent requirements (Resnick 2012, 109); but even so there are limits to how meaningful and protective the process will be (see Cargill 2016 on the impossibility of meaningful informed consent in this context).

Relatedly, many studies ask individuals to give prospective consent for indefinite uses of their samples and data. Such blanket or general consent helps to promote biomedical research by according investigators a great deal of flexibility as compared with reconsenting individuals for each project or trying to anticipate all potential future uses of the samples and data. Soliciting blanket or general consent for the storage and reuse of data and materials—the preferred approach of many researchers—facilitates future research but raises serious ethical issues (Cargill 2016; Resnick 2012; Rothstein 2012). In agreeing, subjects lose control over the ways their data may be accessed and used. Research participants may not fully understand the implications of an agreement to reuse their genetic data, nor is it possible for them to anticipate future research applications, some of which may be objectionable to them.

Tiered or layered consent is a more ethically appropriate approach that gives subjects more options for consenting to the reuse of their samples and data—e.g., no reuse, use for research limited to specific diseases or topics, and/or use acceptable/not acceptable for use in commercial research. Tiered consent can also allow participants to decide whether to allow that their samples or data be shared with other researchers. Researchers using a tiered consent protocol need to keep track of what each subject has consented to, but this can be done electronically.

Strategies to protect the privacy and confidentiality of genomic information stored in biobanks include software protections on particularly sensitive data (such as storing aggregate information only) and sequestering sensitive information (releasing only the data relevant to the particular research project that has been approved by the research subject through tiered consent). The new National Institutes of Health (NIH) Genomic Data Sharing Policy that went into effect in January 2015 provides a model for the protection of genetic data in databases. It requires that all NIH funded research that generates large-scale genomic data obtain participants' consent for their genomic and phenotypic data to be used for future research purposes even if the cell lines or clinical specimens are deidentified. Moreover, the informed consent needs to specify whether the data will be shared through unrestricted or controlled access. Requests for the reuse of data in a controlled access repository will have to be carefully scrutinized to assure the project is consistent with the terms of the informed consent (NIH 2014).

V. RESEARCHERS' RESPONSIBILITIES REGARDING COMMUNICATION OF RESEARCH FINDINGS TO THE PUBLIC

The way genetic risk information about addiction is communicated by researchers will affect the impact of genetic research on individuals and on public health. When researchers disclose results to research subjects, they have a responsibility to clearly communicate what the information does and does not mean, and to avoid providing individual results where these results are not of clear clinical value. Misunderstandings of research, even if unintentional, could also adversely affect community attitudes to addicted persons and their relatives. In addition, it could undermine addicted persons' beliefs about their capacity to reduce or abstain from alcohol consumption. For these reasons a major challenge for genetics researchers is to ensure that the reporting of research on common, non-Mendelian disorders effectively communicates the complex interactions that occur between environmental, social, and cultural factors, and genes in influencing behavior (Wensley and King 2008).

One consideration in conducting genetic research on alcohol-dependent subjects is whether and how receiving genetic information on disease risk will influence an individual's behavior. It is often assumed that giving genetic risk information will prompt individuals to change their behavior in desired directions (Haga, Khoury, and Burke 2003; Hunter, Khoury, and Drazen 2008), but research suggests that this is not usually the case (Khoury 2003; Peto 2001). Indeed, inappropriate communication of genetic risk information may undermine individuals' beliefs about their ability to change their behavior and thus be counterproductive for prevention (Senior, Marteau, and Weinman 2000; Wright, Weinman, and Marteau 2003). It may also raise unnecessary anxiety about disease risk in persons who are in fact at low risk of developing the disorder (Marteau and Croyle 1998).

It has been speculated that genetic explanations may be particularly useful as a coping mechanism among individuals who perceive a risk of substance dependence and who hold fatalistic views about health (Jayaratne, Giordimaina, and Gaviglio 2012). Genetic explanations may also be attractive to individuals who believe that the behavioral changes required to reduce their risk are difficult to enact and/or when they experience threats to their self-image from stigma associated with a condition. Similarly, there is the possibility that persons who are told that they have a genetic variant that confers high protection against alcohol

dependence could believe they could drink as much as they liked without adverse consequences (Spooner, Hall, and Lynskey 2001).

To date, no studies have examined the impact of genetic risk feedback on alcohol consumption. However, one study examined the *intention* to drink alcohol amongst undergraduate students who had been told they had an increased genetic risk of alcoholism compared to those told that they were not genetically susceptible. Participants were led to believe their saliva was being tested and given fake information about their genetic risk. It was found that the provision of information about genetic risk of alcoholism did not affect participants' intention to drink alcohol (Dar-Nimrod, Zuckerman, and Duberstein 2013). There is also the possibility that persons who are told that they are at lower genetic risk of addiction disorders may be less motivated to change their behavior. More research is also needed on whether genetic explanations reduce the willingness of addicted individuals to enter treatment because they believe their disorder is incurable.

One common misunderstanding of genetic research is that having a genetic predisposition to a disorder means one either has, or is very likely to develop, the disorder. When applied to genetic research on addiction, such misunderstandings could lead to unnecessary stigmatization and discrimination of genetically predisposed individuals.

Public misunderstandings of genetic information may in part be a by-product of a lack of health literacy (including genetic literacy) among the general public. The U.S. Department of Health and Human Services estimates that 50 percent of Americans lack what they define as functional health literacy: "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (Institute of Medicine 2004). It is likely that many other countries have similar or even higher rates of health illiteracy.

Rates of population-level genetic literacy are less well established. However, the results of surveys on public understanding of basic genetics suggest that genetic literacy is likely to be even more limited than health literacy. A survey of 1,200 Americans, for example, found that 75 percent incorrectly believed that a single gene could control specific human behaviors (Christensen et al. 2010). Similarly an Australian survey of a representative sample of 1,009 persons found that only a minority correctly understood the meaning of increased genetic risk (Molster et al. 2009).

Researchers have an ethical responsibility not to promote popular misunderstandings and a professional responsibility not to oversell their research results. This calls for humility in professional publications, grant proposals, and in publicly reporting research results. Researchers should also anticipate the role the media will play and seek to minimize the likely misreporting by resisting media pressure to simplify and hype findings. The media often portray the role of genetics in disease susceptibility in a simplistic and deterministic way. For instance, in reporting on genetic research on addiction, media articles often report discoveries of "the gene for addiction." Such reports can reinforce common misunderstandings that people with "the gene" (or even "a gene") are very likely to develop a particular disorder, and that those who do not have it are at low risk of doing so (Khoury et al. 2000).

An overemphasis on the genetics of addiction to which researchers may inadvertently contribute may discourage public policy makers and members of the public from according sufficient importance to environmental factors. A major challenge for genetics researchers as well as for policy makers is to ensure that the reporting of research on common, non-Mendelian disorders effectively communicates the complex interactions that occur between environmental, social, and cultural factors and genes in influencing behavior (Wensley and King 2008). This is particularly true for research on highly stigmatized disorders such as addiction. Failure to do so may result in discrimination against populations in which susceptibility genes are more prevalent. An example of this was the misreporting of the discovery of a "warrior gene" in the Maori population in New Zealand (Lea and Chambers 2007). This research linked a mutation in the MAOA (monoamine oxidase) gene that was highly prevalent in Maori population with alcoholism, violence, criminality, and gambling. It sparked much media controversy and the researchers were accused of using the research to justify discriminatory attitudes towards Maori (Kowal 2015).

Evidence indicates that genetic explanations for alcohol dependence have been growing in popularity across a wide segment of the population (Jayaratne, Giordimaina, and Gaviglio 2012). The challenge for public education on genetic research will be to better explain the personal and public health implications of polygenic disorders in which individual alleles weakly predict risk, and interact with each other and with the person's environment (McBride et al. 2010). Researchers have a role to play in public education through the responsible dissemination of their research results in the community. If successful, such public education could help

to allay some anxieties about third-party misunderstandings of genetic addiction risk because people would understand that this information is not sufficiently predictive of disease risk to be misused in discriminatory ways.

CONCLUSION

While genetic research has the potential to reduce drug dependence and the harms associated with alcohol addiction, these hopes are yet to be realized. Overall, genetic testing is not ready for use in the prediction of drug-dependence liability. Alcohol dependence is a complex, multifactorial, polygenic disorder and the evidence to date shows that it is unlikely that one or even a reasonably small number of genes will be identified that will explain all or even most of its heritability (the fraction of the variance in addiction risk associated with genetic variation). As well as being a product of interactions between multiple genes, alcohol dependence is also a product of complex interactions between genes and the environment. For example, new epigenetic research on alcohol dependence has revealed that external stimuli may influence the expression of genes such that the associations between genes and behaviors will change with different environmental exposure (Nestler 2014; Ponomarev et al. 2012). In light of this, genetic screening is likely to have minimal preventive use over and above advice to drink alcohol in moderation or abstain from alcohol completely. It may be no more effective in predicting disease risk than family history.

Pharmacogenetic testing for responses to treatments, such as that to naltrexone for alcohol dependence, may have more clinical utility than genetic tests for drug dependence liability. Such testing may inform treatment selection and improve treatment outcomes for drug-dependent persons. The evidence linking genetic variants with differential response to treatment, especially to naltrexone treatment, appears at this time to be more robust than that for predictive genetic testing. Given this, pharmacogenetic testing for drug dependence appears to be a more promising prospect for clinical deployment than predictive genetic screening for drug dependence. There are, however, some caveats to this. In the case of naltrexone, the gene that influences naltrexone response is prevalent in some population groups but virtually non-existent in others. This means that the potential for cost-effective positive impacts of pharmacogenetic testing will be restricted to certain population groups. More research is required to demonstrate the utility and cost-effectiveness

of pharmacogenetic testing for drug dependence before it is routinely applied in clinical practice.

We must also be aware of the potential for genetic research on addiction to negatively impact public health if it is miscommunicated or misused. Responsible researchers, and others involved in the work to generate and disseminate the results of this research, should take steps to prevent this from happening. Researchers, the media, clinicians, and the general public must communicate the findings of genetic research about addiction in a responsible and understandable way. This means clearly communicating the complex interactions between genetic, biological, social, and environmental factors involved in addiction. Doing so will help to prevent common misunderstandings about the role of genetics in addiction liability, and hopefully will help to prevent discrimination and stigmatization. A more concerted effort at improving the genetic literacy of the population could also help to achieve this.

Developments in genetic research on addiction are important, but must not be at the expense of investments in social, behavioral, and psychological research on addiction. Likewise, they must not be used to justify a reduced focus on interventions that address the social and cultural determinants of the disorder. Population health strategies such as increased taxation and reduced opportunities to drink alcohol are likely to remain more efficient preventive strategies by reducing risky alcohol use than are high-risk genomic medicine strategies such as genetic screening.

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