
**Introduction**

A genetic contribution to drug dependence has long been suggested by the observation that the disorder ‘runs in families’. Twin and adoption studies have since confirmed that the heritability of drug dependence ranges from 30 to 70%, depending on the drug [1]. This indicates that susceptibility to addiction is influenced by individual genetic make-up as well as environmental factors.

Genomic studies have identified genetic variants that are associated with drug dependence and dependent individuals' responses to various treatments (e.g. naltrexone and acamprosate for alcohol dependence (AD) treatment) (e.g. [2–5]). Optimistic predictions have been made about the potential for these discoveries to personalize medicine [6] and improve the prevention and treatment of substance disorders [7]. As yet, genetic testing has not been used widely in clinical practice because most of the genes identified are only modest predictors of addiction risk or treatment response, and many of these associations have not been replicated widely (e.g. [2,8–10]). A number of commercial companies are none the less offering genetic tests direct-to-consumer (DTC) for predicting susceptibility to alcohol, nicotine and heroin dependence, physiological responses to alcohol consumption (e.g. alcohol flush response, alcohol metabolism) and responses to naltrexone treatment for alcohol dependence. The tests can be purchased over the internet, without any referral by or involvement with a health professional, for as little as $200 (e.g. 23andMe).

This paper aims to:

• describe the DTC genetic tests that are available for addiction-related disorders;
• review the evidence base for these tests; and
• discuss the ethical concerns they raise.

**DTC genetic testing for addiction: what tests are available?**

Table 1 summarizes the DTC genetic tests that are available for addiction-related phenotypes as at January 2011 including, who is offering the test and the genetic variants tested. In the next section we analyse briefly the status of the research for each of these genetic variants.

Table 1. Genetic tests offered direct to the consumer for addiction related disorders/phenotypes by company.

The associations between risk of nicotine dependence in smokers and variants in the CHRNA3, CHRNA5 and CHRNB4 gene cluster that encodes the nicotinic acetylcholine receptors have been well replicated (see [11]). Nicotine binds to these receptors within 60 seconds of inhaling cigarette smoke and produces its rewarding effects indirectly. Smokers with this gene cluster are 1.4 times more likely to develop nicotine dependence than those without [12]. This modest association has only been shown in studies conducted in European samples, however [11]. One of the variants does not exist in African populations, and is present in only one-third of East Asian people [11]. 23andMe acknowledge on their webpage that the test for nicotine dependence is only applicable to Europeans, but deCODE does not.

Significantly, the test provides information only about risk of nicotine dependence in current smokers. It does not provide any information about the risk of nicotine dependence in non-smokers (e.g. smoking initiation and abstinence). The clinical utility of such a test is questionable, given that...
smoking carries significant negative health consequences regardless of whether the smoker develops nicotine dependence. This test is of limited value to the smoker whose money could be better spent investing in smoking cessation assistance.

Alcohol flush response: aldehyde dehydrogenase (ALDH2*2)

Three companies test for alcohol flush response by screening for the ALDH2*2 allele. This allele produces an inactive ALDH2 enzyme that allows acetaldehyde (a by-product of alcohol metabolism) to accumulate in the body producing facial flushing, sweating and headache. In more severe cases, it can cause cardiovascular collapse, arrhythmias, unconsciousness and convulsions. These aversive symptoms protect against developing AD. Carriers of two copies of this allele (homozygotes) have a 10 times lower risk of AD, but are rare [2]. Heterozygotes who carry one copy of ALDH2*2 have a fivefold reduction in risk of AD [2].

While ALDH2*2 appears to be associated with significantly lower risk of AD, it occurs mainly in East Asians (about 30% prevalence), with cases in European and African populations being rare. From the information that is publicly available, none of the DTC genetic testing companies appear to inform prospective consumers of this.

The clinical and economic utility of this test with adults is also doubtful. First, in western cultures where alcohol use is ubiquitous, people positive for ALDH2*2 will not need a genetic test to tell them that small quantities of alcohol make them flush. Secondly, those who test negative for ALDH2*2 may be under the misapprehension that they can drink without harm or risk of addiction. This is of particular concern because of evidence that moderate drinkers with ALDH2*2 have an increased risk of developing oesophageal cancer [13].

AD: Taq1A polymorphism of dopamine 2 receptor (DRD2)

Variants in the DRD2 mediate the rewarding effects of alcohol, as well as many other drugs of addiction [5]. The Taq1A polymorphism of DRD2 has been linked most consistently to AD. Meta-analyses suggest that people with Taq1A are 1.3 times more likely to develop AD than those without [14,15]. However, recent evidence suggests that Taq1A maps onto an adjacent gene (ANKK1) [9], prompting questions about whether Taq1A increases AD risk or is a marker of a region where multiple alleles involved in AD risk are located. Meta-analyses suggest that publication bias may have influenced initial optimism about the strength and significance of the association, which varies between different populations [14]. The results of the test for AD using this single nucleotide polymorphism (SNP) should therefore be interpreted with caution.

Response to naltrexone treatment of alcohol dependence: μ-opioid type 1 receptor (OPRM1)

23andMe offers a genetic test that purports to predict an individual's response to naltrexone treatment for AD. The use of genetic information to target medical treatment is called pharmacogenetics. OPRM1 mediates AD individuals' response to treatment with naltrexone; a drug that blocks opioid signalling and blunts the euphoria associated with alcohol consumption (e.g. [16]). Individuals with the Asp40 allele of OPRM1 are three times more likely to respond to naltrexone therapy for AD than those homozygous for the Asn40 allele [3,17,18]. Such tests have the potential to significantly improve the effectiveness of naltrexone treatment of AD, given that it is only marginally effective in the AD population [19]. Because naltrexone is a prescription drug, there is a good case for restricting such pharmacogenetic tests to use in clinical contexts. However, there are few guidelines to address the ethical issues raised by the application of such tests [20].

Heroin dependence: OPRM1

Asp40 has also been claimed to predict the risk of developing heroin dependence, but results are conflicting [21]. Asp40 was more prevalent among heroin-dependent people in two studies (odds ratios of 2.9) [22,23], but in two other studies it was more prevalent in people without heroin dependence [24,25]. As the majority of studies of Asp40 show no association with heroin dependence [21], it is premature for 23andMe to be offering tests for this variant. The association between Asp40 and naltrexone therapy for AD appears to be more robust, but caution is still needed in interpreting
test results because other environmental or epigenetic factors may affect whether this genotype predicts better treatment outcomes.

Ideally, consumers should be told about the population prevalence of the genes that are tested. This is particularly pertinent for these tests because Asp40 is much more common in people of Asian descent (about 48%) than in Americans of Caucasian (15–18%) or African American descent (5%). An African American person contemplating a genetic test for naltrexone response or susceptibility to heroin dependence may decide not to be tested because the gene has limited predictive power, and the predictive variant only occurs in 5% of such people.

Ethical concerns about DTC genetic testing for addiction

Predictive power, reliability, validity and clinical utility

The genes tested for by DTC companies have limited predictive power for addiction liability. With the exception of the gene for alcohol flushing, the effect sizes for each of the above-mentioned genes are small, the associations have not been well replicated and the prevalence of some of the alleles are very rare in certain cultural groups, limiting their power to predict addiction liability. In the case of nicotine dependence, there is evidence that genetic risk information does not improve upon predictions based on family history [26]. The validity of DTC tests is undermined further by evidence showing that the same tests produced contradictory disease risk estimates when administered by two different companies, and in some cases tests results were inconsistent with the patients' actual disease status [27].

The ethical defensibility of these DTC tests is brought further into question by the fact that they do not give the consumer clinically actionable information. In practice, someone who tested positive for a gene associated with heightened risk of AD would be advised to drink in moderation, good advice regardless of genetic risk. Similarly, recommending that individuals quit smoking and not use heroin are public health messages that should be given irrespective of genetic risk. Pharmacogenetic tests for response to naltrexone provide more clinically useful information, although such tests would be best administered by the physician prescribing naltrexone and counselling should be given about the meaning of test results.

Genetic counselling and test interpretation

A clinically useful genetic test would yield actionable information to prevent disease and improve health, e.g. by undertaking a pharmacological, behavioural or psychological intervention. None of the DTC tests for dependence liability meet these criteria. Most are provided with uninterpreted genetic risk information that, at best, advises consumers that their risk of developing dependence is average, or slightly above or below average. Most companies do not offer genetic counselling either before or after testing (Navigenics is the exception, but it does not offer genetic testing for addiction-related phenotypes). It is unlikely that the average consumer would be able to understand their genetic tests results. A recent survey of potential DTC genetic test consumers found that most did not understand their test results and 78% indicated a need to consult a general practitioner (GP) or physician to help interpret them [28].

DTC tests that offer no genetic counselling and limited interpretation of results are likely to create additional work for GPs and physicians who will be asked to interpret and clinically manage these test results. This is problematic for two reasons. First, it creates additional costs and pressure on an already stretched health system. Secondly, many clinicians lack the knowledge, skills and education to interpret genetic test results accurately [29]. Even if they were able to interpret the test result accurately, they may feel pressured to provide a therapeutic intervention to prevent the development of a disease when the patient's level of risk is average.

Discrimination and privacy
DTC genetic tests raise many of the same privacy issues as tests administered in clinical and research contexts. The results of DTC genetic tests may be misused by third parties, such as health insurance companies and employers to justify discrimination, or by the criminal justice and legal systems to link individuals to crime [30]. DTC companies may be legally required to communicate or disclose genetic information to these third parties under subpoena.

Some countries have introduced legal safeguards to minimize such discrimination. For instance, in the United States, the 2009 Genetic Information Non-Discrimination Act protects asymptomatic individuals who have a genetic mutation against discrimination by health insurers and employers. The Act prohibits health insurers from using genetic information or requesting testing in setting insurance premiums or employers from using it in decisions about hiring, promoting or firing an employee [31]. However, it does not cover life, long-term care or disability insurance; nor is it applicable to people who have clinical symptoms of a genetically based disease. Consequently, the potential for genetic discrimination still exists. The legislation has also yet to be tested in the courts, so it is not clear what level of protection it offers. However, because alleles for addiction susceptibility are nowhere near as predictive as those for single gene disorders (e.g. Huntington's disease), discrimination on the basis of these alleles is unlikely.

Proponents of DTC genetic testing argue that it offers more privacy protection than genetic testing ordered via a medical professional because test results will not be included in the person's medical record that may be subject to subpoena (e.g. [29]). This claim is contestable. The security and privacy of any online transactions, including the purchasing of genetic tests, is not guaranteed, with hacking and identity theft possibilities [32]. Furthermore, the companies who offer DTC testing are not subject to the privacy restrictions of the Health Insurance Portability and Accountability Act (HIPAA), although most claim to be ‘HIPAA-compliant’. [33]. If DTC companies are not being HIPAA-compliant, consumers may not have rights to access their genetic information or to request corrections to it. Their genetic information may also be vulnerable to misuse by associates of DTC companies, who may be able to access genetic databases but are not contractually required to protect their privacy [34].

Informed consent

It is more difficult to ensure informed consent to DTC testing than to clinical genetic tests, because there is no health professional acting as an intermediary to authorize and support the collection of DNA. Accordingly, there is less quality control in the collection of specimens. An individual may also take a DNA specimen from another person (e.g. through hair strands, a used cotton tip, cigarette butts) and send it to a DTC company without that person's consent. This is referred to as non-consensual, or surreptitious, testing. It is unclear how common it is [35]. None the less, it could be ameliorated by having some enforceable minimum standards for obtaining informed consent (i.e. the person being tested would have to sign consent forms and provide signed copies of identification) and the samples (e.g. by companies refusing to analyse specimens other than a vial of saliva or a cheek swab). The United Kingdom has made non-consensual analysis of DNA an offence under the Human Tissues Act [36].

Testing of minors

The consensus in published guidelines is that genetic testing of asymptomatic children should be postponed until they are able to make an informed choice about such testing [37,38]. For DTC genetic tests, there is no consistent policy on testing minors. A recent analysis of DTC genetic companies’ websites revealed four different approaches to testing minors [38]. One group of companies provided no information at all about testing minors. A second group allowed genetic testing of minors, if authorized or requested by their parents/guardians (e.g. deCODE and 23andMe). A third group made clear that their website is not ‘directed to minors’, but do not explicitly refuse to test minors if parents
request it (e.g. Biomarker Pharmaceuticals). A fourth group states that people must be 18 years or older to be tested (e.g. Navigenics).

Genetic testing for addiction liability during childhood is difficult to justify, given the poor predictive value of these tests. We would recommend that DTC genetic tests not be offered to people under the age of 16 years. Until DTC genetic tests are regulated, this standard will be difficult to enforce.

Misrepresentation

The promises made by different companies about the utility of DTC genetic testing may vary. Not all DTC testing companies promise the same personalized health-care services from their genetic tests [39], with some promoting them only as a product for consumers to satisfy their curiosity. A major problem with DTC genetic tests being promoted for clinical use is that there is often a significant gap between the claims made by providers about their clinical usefulness and the research evidence about this [27]. This is misleading marketing. Many companies’ websites, for example, include disclaimers that test results are not diagnostic and should not be considered as medical advice, but a Government Accountability Office (GOA) audit found that company marketing materials, and company representatives, often highlighted the clinical implications of the tests [40]. Moreover, it found that 10 of the 15 DTC genetic testing companies audited engaged in ‘some sort of fraudulent, deceptive or otherwise questionable marketing practices’.

In the United States, federal law prohibits companies from using unfair, deceptive or fraudulent trade practices, or making false or misleading advertising claims [41]. In theory, this law prohibits false genetic-testing claims, but in practice fair-trade commission regulators may lack the knowledge that enables them to assess when the claims made by DTC genetic testing are misleading. This suggests the need for DTC genetic testing companies to be regulated and for their tests to be subject to pre-market review.

The case for regulation

There is a need for a regulatory framework to better protect consumers of DTC genetic tests. This framework would need to consider: the clinical validity and utility of the tests, the quality of genetic counselling offered to consumers, protecting consumer privacy and minors, minimizing risks of non-consensual testing and preventing misleading claims. Researchers, doctors, lawyers, bioethicists and policy makers have advocated for the regulation of DTC genetic tests for some time [42], and multiple ad-hoc task forces have examined the issues that need to be addressed by regulation [43]. In spite of this, no concrete action was taken on regulation until 22 July 2010, when the US Food and Drug Administration announced its plans to regulate DTC genetic tests [42]. This announcement coincided with the US GAO review of DTC tests, which concluded that DTC test results were misleading and had limited clinical value [40].

Conclusion

While different DTC genetic testing companies may promise different outcomes from their tests, in general genetic tests have been commercialized prematurely with little oversight, regulation or respect for scientific rigour [43]. There is often no intervening period in which test results are replicated and clinically tested before being commercialized. In the case of genetic tests for addiction liability and treatment response, tests are commercially available that have failed to demonstrate clinical validity and utility, and which test for variants that are rare in some population groups. This information is not being communicated to consumers, who may have the expectation that these tests are clinically relevant. Consequently, they will be unable to make well-informed choices about whether to undergo these tests or interpret the information the tests can reliably provide them with. Moreover, because genetic counsellors and medical professionals are not typically involved in the disclosure of DTC genetic test results, there is the potential for consumers to misinterpret their test results. This, in turn,
may cause harm by making them unnecessarily anxious and prompt them to pursue unnecessary medical interventions, or mislead them into believing that they can consume alcohol, heroin or nicotine with a low risk of developing dependence. Until DTC tests for addiction are regulated, their potential for harm is likely to exceed their limited potential to prevent addictive behaviour or reduce the harms of drug use.

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