Published in final edited form as:
Int J Neuropsychopharmacol. 2012 November ; 15(10): 1547–1557. doi:10.1017/S1461145711001982.

Ethics and Neuropsychiatric Genetics: A Review of Major Issues

Steven K. Hoge, MD and **Paul S. Appelbaum, MD**
Division of Law, Ethics and Psychiatry and the Center for Research on Ethical, Legal and Social Implications of Psychiatric, Neurologic, and Behavioral Genetics, Department of Psychiatry, Columbia University Medical Center

Abstract

Advances in neuropsychiatric genetics hold great hopes for improved prevention, diagnosis, and treatment. However, the power of genetic testing to identify individuals at increased risk for disorders and to convey information about relatives creates a set of complex ethical issues. Public attitudes are inevitably affected by the shadow of eugenics, with its history of distorting scientific findings to serve socio-political ends. Nonetheless, the growing availability of genetic tests means that more patients will seek genetic information, and physicians must manage the process of informed consent to allow meaningful decisions. Patients should be helped to understand the often-limited predictive power of current knowledge, potential psychological impact, risks of stigma and discrimination, and possible implications for family members. Decisions for predictive testing of children raise additional concerns, including distortions of family dynamics and negative effects on children's self-image; testing is best deferred until adulthood unless preventive interventions exist. Pharmacogenomic testing, part of personalized medicine, may bring collateral susceptibility information for which patients should be prepared. The implications of genetic findings for families raise the question of whether physicians have duties to inform family members of implications for their health. Finally, participation in research in neuropsychiatric genetics evokes a broad range of ethical concerns, including the contentious issue of the extent to which results should be returned to individual subjects. As genetic science becomes more widely applied, the public will become more sophisticated and will be likely to demand a greater role in determining social policy on these issues.

Keywords

ethics; genetics; consent

Address correspondence to Dr. Appelbaum at Department of Psychiatry, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 122, New York, NY 10032. Phone: 212-543-4184; Fax: 212-543-6752; psa21@columbia.edu.
Dr. Hoge is Clinical Professor of Psychiatry and Director, Forensic Psychiatry Training, Department of Psychiatry, Columbia University. Dr. Appelbaum is the Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, and director of the Center for Research on Ethical, Legal and Social Implications of Psychiatric, Neurologic, and Behavioral Genetics, Department of Psychiatry, Columbia University.

Statement of Interests
None

Introduction

Over the course of the last sixty years, tremendous progress has been made in the science of genetics, from unraveling the mystery of DNA's double helix to the triumph of mapping the human genome. These successes have stirred the hopes of scientists, physicians, and the public, each group's imagination fired by differing facets of the potential of genetic information. Scientists using the metaphor of the genome as a blueprint or map hope to leverage this information to better understand complex biological processes (Green & Guyer, 2011). Physicians anticipate that the new genetic science will lead to greater diagnostic capabilities, superior therapeutics, and earlier preventive interventions (Lawrence & Appelbaum, in press). The lay public, not unmoved by the technological promise, has found in genetics an explanation for the strong links that connect biological relatives, including otherwise inexplicable commonalities of verbal expression, complex behavior, and personal quirks (Richards, 1996).

In this article, we review the major ethics issues raised by advances in neuropsychiatric genetics. It should be recognized that this discussion of ethics reflects current thinking about how genetic information should be used. But we are still early in the evolution of this promising technology and it will be many years before its full impact is felt and understood by society. Only then will it be possible to determine how genetic science should best be used to benefit society, and to fully understand the ethical implications of that use. As experience is gained in the real world, ethical principles will emerge to guide the use of genetic information in ways that balance the interests of individuals and society.

Historical Background: The Specter of Eugenics

Clinicians and researchers generally have positive views of genetic research, anticipating dramatic improvements in understanding the causes of mental disorders, selecting appropriate treatments for patients, and preventing or reducing the burden of illness. But many lay people, particularly members of minority groups, react to genetic science with suspicion, the roots of which can be traced to the historical specter of the eugenics movement (Bates et al., 2005). The term eugenics (literally, "well born") was coined by Sir Francis Galton (1883), who was influenced by the publication of *Origin of Species* by his half-cousin Charles Darwin. Galton posited that progressive social policies had undermined natural selection by providing protection, support, and sustenance to the "unfit," which allowed them to survive and reproduce. Inevitably, he believed, the population or "race" would degenerate unless countervailing social policies were adopted. The eugenics movement that developed from these ideas was based on the belief that scientific methods should be applied to improve the genetic stock of mankind. The movement quickly spread to the United States, then to nations around the world (Black, 2008).

Positive eugenics programs promoted marriage and reproduction among those believed to have superior genes, for example by providing financial incentives to identified couples to have another child. Negative eugenics approaches aimed to lower the birth rates of those with "undesirable" characteristics. The U.S. was in the vanguard of negative eugenics. Early evidence of the heritability of "insanity" and "feeblemindedness" led many states to ban marriage and to compel sterilization of individuals in these affected groups (as well as criminals), beginning in 1907 (Black, 2008). Approximately 65,000 people in 28 U.S. states underwent compulsory sterilization for eugenic purposes before these programs were halted. During the eugenics era, numerous other nations enacted compulsory or coercive sterilization programs that targeted in various combinations the mentally ill, mentally retarded, criminal offenders, and those afflicted with inherited medical disorders, including

Germany, Canada, Japan, Sweden, Finland, Iceland, Norway, and Switzerland (Bashford and Levine, 2010).

Under the Nazi regime's eugenics program, Germany involuntarily sterilized more than 350,000 individuals, primarily persons with schizophrenia, mental retardation, and alcoholism (Hassenfeld, 2002; Meyer, 1988). The Nazis also called on physicians to identify children and adults with a variety of heritable disorders ("life unworthy of life") for extermination. More than 70,000 psychiatric patients were put to death in this Aktion T4 program. Later in the war, 200,000–300,000 additional psychiatric patients were killed by gunshot, starvation, and other methods, often to provide hospital beds to accommodate war casualties (Meyer 1988; Torrey and Yolken, 2010). Following World War II, eugenic policies were discredited and gradually abandoned in most countries, although involuntary sterilization of institutionalized individuals persisted in the United States until 1981 (Sullivan, 2002). However, the eugenics movement is a cautionary example of how the power of genetic science and its predictive promise can be exaggerated, distorted, and channeled by elites to justify unspeakable actions. Wherever they were applied, eugenic laws disproportionately affected the less powerful segments of society, including the poor and minorities. It is not surprising that these groups remain the most leery of genetic research and its potential applications. Nor is it surprising that there is lingering concern about the motives of physicians who recommend genetic testing, the extent to which that information may be shared, and how it may be used.

Clinical Applications of Genetic Tests in Adults

Genetic testing can be used in clinical practice to: establish more definitive diagnoses ("diagnostic testing"), assist in management decisions ("pharmacogenomic testing"), provide guidance for reproductive choices ("reproductive testing"), and estimate the likelihood of disease onset in the future ("predictive testing"). At present, the frequency of genetic testing in neuropsychiatric practice varies considerably based on the disorder involved and the purpose for which testing is sought. Diagnostic testing is most commonly used by clinicians who care for patients with neurodevelopmental disorders, where it may also aid reproductive planning (Miller et al., 2010); to confirm diagnoses of neurodegenerative disorders, including Huntington's disease (U.S. Huntington's Disease Genetic Testing Group, 2003), frontotemporal dementia (Goldman et al., 2004) and autosomal dominant forms of Alzheimer's disease (Goldman et al., 2011); and for several syndromes associated with psychosis (Bassett et al., 2003) and epilepsy (Ottman et al., 2010). Pharmacogenomic testing for individualized treatment decisions is still at an early stage of development, without a robust evidence base to support its common use, and hence tends to be infrequent (Arranz & Kapoor, 2008). Reproductive testing is most useful for autosomal dominant disorders, such as Huntington's disease, and for X-linked disorders, including Fragile X syndrome (Garber et al., 2008), given the low predictive power of most genes associated to date with common psychiatric and neurodegenerative disorders. For the same reason, predictive testing, although much discussed, plays a relatively small role in most neuropsychiatric disorders at present, with the notable exception of some autosomal dominant neuropsychiatric disorders like Huntington's disease.

However, clinical genetic testing is likely to become increasingly common in many neuropsychiatric settings for three reasons. First, preliminary research suggests that there may be significant latent demand for testing. For example, surveys of relatives of affected individuals indicate that many of them would seek genetic testing to determine their risk—or that of their children or other relatives—for developing neuropsychiatric disorders, or to aid in reproductive decisions (Jones et al., 2002; Meiser et al., 2008; Milner et al., 1998; Smith et al., 1996; Trippitelli, 1998; Wilde et al., 2011). DeLisi and Bertisch (2006) found that

83% of family members of schizophrenia patients who had participated in genetic research would seek predictive testing if it were available, and 80% of the spouses of bipolar disorder patients indicated that they would want to be tested if a genetic test for the condition were available (Trippitelli et al., 1998).

Second, genetic tests are becoming more widely available. Advances in research have resulted in the identification of a growing number of genetic variants associated with neuropsychiatric disorders, and the potential demand for such tests has encouraged their commercialization. In addition to traditional clinical laboratories, for-profit genetic testing companies have initiated aggressive direct-to-consumer (DTC) marketing campaigns for a broad range of tests (Hogarth et al., 2008). These marketing efforts can be problematic. Gollust and colleagues (2002) found that DTC advertisements overstated the value of testing, provided misinformation about genetics, endorsed a deterministic relationship between genes and disease, and tended to exploit consumers' fears to drive demand. In addition, a study by the U.S. Government Accountability Office (2010) called into question the accuracy of DTC test results. Whatever its faults, DTC marketing is likely to increase public awareness of and demand for testing.

Third, as genetic testing migrates from research protocols to ordinary clinical settings, access to tests will not be determined by restrictive protocols, but by physicians, with many likely to comply with patients' requests to know their genetic status, even if it is not highly predictive of future disease. Moreover, the widely anticipated introduction of whole genome sequencing into clinical medicine will make available to physicians and patients data on their complete genetic make-up, including variants associated with neuropsychiatric disorders. This evolution of technology for genetic testing seems likely to magnify the presence of genetic information in the clinical setting (Ashley et al., 2010).

Ethical Challenges in Genetic Testing of Adults

As genetic testing moves into the clinic, the most salient ethical concerns will center on promoting informed decision making by patients. Clinicians will need to be prepared to engage with their patients in discussing the risks and benefits of genetic testing, a process that will be complicated by several factors. Few neuropsychiatric conditions follow classical Mendelian inheritance (Huntington's disease and autosomal dominant forms of dementia and epilepsy are among the exceptions). In general, the picture is much more complex. To the extent that single nucleotide polymorphisms (SNPs) have been associated with disorders such as bipolar disorder, schizophrenia, and depression, each variant contributes only very modestly to individual susceptibility (Plomin and Davis, 2009). For example, the associations between single genes and psychiatric disorders such as schizophrenia, bipolar disorder, bulimia, anorexia nervosa, and attention deficit disorder, have odds ratios of 1.1 to 1.6 (Kendler, 2006). With respect to schizophrenia, genetic loci that have been identified and replicated have relative risks of about 1.1 (Kim et al., 2011). At present, testing for SNPs has no clinical value for these common disorders. On the other hand, recent data suggest that up to 2.5% of people with schizophrenia may have copy number variants (CNVs) associated with much higher odds ratios (Tam et al., 2009; Walsh et al., 2008), though penetrance may still be incomplete and variable (Vassos et al., 2010). And testing for CNVs among children with neurodevelopmental disorders is rapidly becoming the standard of care (Miller et al., 2010). One of the more common and predictive variants is the microdeletion on chromosome 22q11.2 associated with velocardiofacial syndrome (DiGeorge syndrome)a. Approximately 25% of individuals with the deletion develop schizophrenia (Bassett et al., 2003). Yet even this abnormality is relatively rare, with an estimated prevalence of about 2% in individuals with schizophrenia (Murphy, 2002).

Another complicating factor is emerging evidence suggesting that for some conditions genetic predispositions by themselves may not result in the development of disorder, unless they interact with appropriate environmental conditions and life events (Thapar et al., 2007). For example, genetically determined variation in the production of the enzyme monoamine oxidase A (MAOA) appears to interact with childhood maltreatment to increase the rates of antisocial behaviors occurring later in life (Caspi et al., 2002; Beach et al., 2010). Similar, albeit controversial, findings have been offered for the impact on depression of serotonin transporter polymorphisms, with the development of the disorder reported to be heightened by the occurrence of substantial life stress (Caspi et al., 2003; Munafo et al., 2009). Experimentation with animal models (Weaver, et al., 2004) and analysis of post-mortem tissues (McGowan, et al., 2009) has suggested that stress, such as childhood abuse, may impact gene expression through epigenetic modification. Further complicating attempts to identify the effects of gene-environment interactions are findings indicating that people may preferentially seek or create their own experiences, based in part on their genetic endowment, a phenomenon referred to as genotype-environment correlation (Kendler and Baker, 2007). More precise quantification of the genetic contribution to these—and perhaps other—psychiatric conditions awaits the disentanglement and verification of gene-environment effects (Duncan and Keller, 2011).

Given these limitations, in many cases an important part of the consent process will be informing those interested in testing that the results are likely to be indeterminate and result in relatively small adjustments to their estimated likelihood of having, developing or passing on a condition. At present, for most people risk probabilities will be more strongly affected by past history, family history, clinical factors, and demographic variables. In the event that testing is pursued in these situations, the responsible professional must be prepared to face a wide range of patient capabilities related to numeracy and understanding of risk. Given the documented difficulties that patients have in understanding genetic information (Klitzman, 2010b), instruction in probability using simple aids has been suggested (Faraone et al., 1999; Hodgkinson et al., 2001). The development of counseling techniques and decision making aids will become an increasing priority as the number and range of genetic tests continue to grow (Austin and Honer, 2007). With the anticipated introduction of whole genome sequencing into clinical practice in the next decade (Pasche and Absher, 2011), the urgency of developing means to help cope with the data is even greater.

In making the decision to be tested, individuals must also take into account potential negative consequences. With regard to predictive testing, for example, test results indicating an enhanced propensity for neuropsychiatric disorder can profoundly affect self-image, potentially leading to increased anxiety and depression (Wilhelm et al., 2009). In part, concern over these negative consequences is driven by the stigma associated with neuropsychiatric conditions, which may extend to asymptomatic carriers and family members (Phelan, 2005). Compounding the difficulties in dealing with test results is the reality that an individual whose results indicate enhanced propensity for developing a disorder still faces substantial uncertainty that the disorder will develop at all or, if it does, what its severity will be. The uncertainties are further magnified by the fact that many disorders will appear only later in life and truly effective prevention and treatment are unavailable. If reproductive planning decisions drove the choice to be tested, the results may be equally indeterminate. Thus, genetic information may leave individuals subject to considerable confusion and stress when making decisions about prophylactic interventions, including life-style changes, participation in high-risk research, and family planning.

Moreover, genetic information may be put to discriminatory uses. In the U.S., the Genetic Information Non-Discrimination Act of 2008 (P.L. 110–233, 122 Stat. 881) (GINA) provides federal protection against discrimination based on genetic information (including

family history) in health insurance and employment. However, GINA does not extend to life, disability, long-term care or other forms of insurance or to genetic conditions once they become manifest (Appelbaum, 2010). Physicians can reduce the risk of discrimination against their patients by warning them as part of the consent process about the various ways that discrimination could be manifested, which may lead them to greater caution in seeking genetic information. Altering the source of the test is another option. Test data obtained through a hospital laboratory or other health care entity are likely to reside in an information system that may be accessed by other health care providers and perhaps others. An alternative is testing in a private laboratory from which patients may obtain test results and discuss them with their physicians without including them in the medical record. Of course, genetic information will then not be available to subsequent treaters, with potentially negative impact on patients' health (Klitzman, 2010a).

Even when definitive results are available, some people will prefer not to shoulder the burden of knowing their future or the risk of conceiving children with a propensity for a disorder, and will forgo the prognostic capabilities of modern medical technology (Kass, 2004). For other patients, the negative consequences will be of less importance that the availability of clinical interventions or greater diagnostic certainty. In a review of the literature, Marteau and Croyle (1998) found that only about 10% of those at risk for Huntington's disease, for which there is no effective intervention, elect to undergo predictive testing. However, among women at risk for breast cancer, a disease for which preventive measures and treatment are available, about 50% choose to have susceptibility testing; similarly, about 80% agree to be tested for familial adenomatous polyposis, for which effective prophylaxis exists.

Some authorities in the field, including the influential Nuffield Council on Bioethics (1998) have taken the stance that the decision to offer or to recommend genetic testing should turn on two factors: the availability of effective interventions for the tested disorder and the predictive accuracy of the test (see also Burke, Pinsky & Press, 2001). This approach has led major professional organizations to take the position that apolipoprotein E gene (APOE) testing for susceptibility to late-onset Alzheimer's disease (AD) is not clinically indicated (Goldman, et al., 2011). The test is only modestly predictive—studies indicate a roughly 3-fold risk for AD with one copy of the E4 allele and a 12-fold risk for those with two copies. Approximately half of those with late-onset Alzheimer's disease have one or more copies of the E4 allele, which is present in about 25% of normal controls (Verghese et al., 2011). Thus, many people who carry the E4 allele will not develop AD and may suffer undue worry from test results, and many of those who test negative for it will develop the disorder and may feel falsely reassured by their genotype. And, of course, prophylactic interventions are not available. Of note, APOE4 is among the most predictive polymorphisms detected in association studies of common variants in neuropsychiatric disorders, underscoring the limitations of testing for these polymorphisms in general.

Recent results from a controlled study suggest that some concerns about the effects of disclosure of APOE status—and by extension perhaps other polymorphisms predisposing to disorders with similar characteristics—may be exaggerated, at least over the short-term. In the REVEAL study, Green and colleagues (2009) investigated the adult children of patients with AD. The control group received a risk assessment for developing AD based on age, gender, and being a first-degree relative of an affected individual. The study group received the same information plus their APOE genotype-specific risk. Participants were assessed for anxiety, depression, and test-related distress at six weeks, six months, and one year. No differences between groups were found. However, those who tested positive for the E4 allele had a significantly higher level of test-related distress when compared to those who tested negative for the allele, though the former group was no less likely to say that they would

undergo testing again (Zick et al., 2005). Whether the results from this highly selected sample will apply to the general population remains unknown.

In the absence of a clear consensus for most disorders, it is likely that many physicians currently approach genetic testing on a case-by-case basis. In some instances, physicians may only address genetic testing when their patients present with test results in hand, looking for information and guidance from a trained professional. In other instances, clinicians may choose to initiate discussions of the risks, benefits, and limitations of genetic testing. What principles should guide clinical practice? We have a preference for involving patients in the decision-making process regarding potential testing and, when testing is performed, providing information regarding results to the fullest possible extent. As part of this decision-making process, patients will need to be made aware of the risks as well as the benefits of testing (Finn & Smoller, 2006). This is consistent with a respect for the decisional autonomy of patients, even when their choices are contrary to professional recommendations. How best to do that without engendering unnecessary anxiety that can compromise decisional abilities is an important area for ongoing research; models include the REVEAL study described above disease (Green et al., 2009) and Wilhelm et al.'s (2009) study of disclosure of data related to depression risk. Research is also needed to help clarify patients' abilities to understand the complexities of genetic testing and to identify methods to improve understanding. However, even in the absence of established interventions to alter the course of disease progression, it is reasonable to anticipate that many patients will have legitimate reasons for seeking genetic tests and sufficient comprehension of potential results to justify proceeding.

To guide their patients through the decision-making process, clinicians will need to be knowledgeable about emerging genetic findings. Indeed, in all but the largest referral centers, this burden is likely to fall on those physicians who are directly involved in caring for patients, since the very small number of genetic counselors (approximately 2400 certified genetic counselors in the U.S. (American Board of Genetic Counseling, 2011) means that they generally will not be available to play that role. At present, most clinicians are not prepared to perform this task. There is evidence that physicians, in general, are not well informed about genetic testing (Menasha et al., 2000; Baars et al., 2005). A survey of psychiatrists revealed a low level of knowledge regarding psychiatric genetics, with less than one-quarter feeling competent to discuss genetic information with patients and families (Finn et al., 2005). In the mental health field, many patients are treated by non-physician clinicians who are likely to have even less knowledge of genetics. Patients and family members may have difficulty gaining access to professional guidance regarding genetic testing. Major educational efforts will need to be addressed to the relevant clinical disciplines, especially given current evidence of the inadequacy of training in genomics in psychiatry (Hoop, et al., 2010; Winner et al., 2010).

The anticipated introduction of whole genome (or exome) sequencing to clinical medicine will complicate the process of obtaining consent and returning results to patients. It will not be possible to fully inform patients about the possible findings and their implications, since literally any component of the genome could be involved. Moreover, many of the findings are likely to have unclear import for the patient's health and reproductive choices. One approach may involve helping patients to decide what kind of information they would like to receive by stratifying consent, e.g., asking them whether they want to know information that is clinically actionable, has reproductive implications, may affect life planning, etc. The National Genome Research Institute (2011) has funded a set of studies to examine return of genomic data from research settings that should provide guidance for the clinical context as well.

Prenatal Genetic Testing

At present, prenatal genetic testing is available through preimplantation genetic diagnosis (PGD) for couples utilizing *in vitro* fertilization (Klitzman et al., 2008), but is more commonly performed on samples obtained by amniocentesis or chorionic villus sampling for chromosomal abnormalities (e.g., Down syndrome) and single-gene conditions (e.g., Huntington's disease, fragile X syndrome). However, the development of technologies for the detection of fetal chromosomal abnormalities in maternal serum (Chiu et al., 2011), with indications that reliable detection of genetic polymorphisms may be possible (Lo et al., 2010), is likely to encourage greater use of prenatal testing (Greely, 2011).

Preliminary studies suggest there is a substantial interest in prenatal testing for other neuropsychiatric disorders such as bipolar disorder (Jones et al., 2002; Smith et al., 1996; Trippitelli et al., 1998), schizophrenia, alcoholism, attention deficit disorder, and depression (Milner et al., 1998). The high level of expressed interest in prenatal testing may reflect a lack of understanding of the likely value of predictive testing for these conditions. For example, a genetic test that suggests a doubling of lifetime risk for developing schizophrenia —higher than is currently feasible (with the exception of 22q11 deletion syndrome and rare, highly penetrant variants within families)—would raise the probability from 1% to 2%--a high relative risk, but still a low absolute risk. Even if prospective parents vary considerably in how heavily to weigh the risk of neuropsychiatric illness in their decisions to abort pregnancy, this level of predictive power is not likely to provide much helpful information to them.

The potential systematic use of prenatal testing for psychiatric disorders raises concern about the impact on the gene pool as well. For example, there is some evidence that vulnerability to bipolar disorder is linked to creativity (Jamison, 1993), propensity for depression to greater deliberation (Soliman et al., 2011), and susceptibility to schizophrenia to skills in mathematics (Karlsson, 2004). Thus, widespread use of prenatal testing might reduce not only the prevalence of affective disorder, but also the level of creativity in the arts, sciences, music, literature, philosophy, and math. In contrast to the ethos of the eugenics era, it is now generally recognized that "it makes no evolutionary sense to drive our species through a man-made bottleneck of genetic uniformity" (Brosius and Kreitman, 2000). However, given a societal commitment to personal choice in reproductive decisions, it is not clear how the interests of potential parents should be reconciled with those of society to maintain a diverse gene pool. The potential risk to the diversity of the gene pool cannot be quantified at this time and ultimately will be determined by the extent to which prenatal testing is employed and the degree of uniformity of individual reproductive decisions. However, ongoing discussion may allow appropriate policies to be fashioned in advance of evident problems.

Genetic Testing of Children

Genetic testing of children may be diagnostic or predictive, and each scenario has different ethical implications. Diagnostic genetic testing as part of an evaluation of an existing condition is the least problematic, but can raise issues regarding impact on family members. For example, testing for fragile X syndrome may reasonably be included in the evaluation of a child with developmental delays. Such testing contributes to the diagnosis of a child with evident impairment, allows for planning treatment interventions, and permits the parents to make future reproductive decisions. Even here, however, identification of a child with fragile X syndrome may have unwelcome implications for unaffected parents who carry the premutation (a smaller number of trinucleotide repeats than are found in clinical cases); males may be susceptible to tremor/ataxia syndrome later in life (Leehey, 2009) and females

to premature ovarian failure (American College of Obstetricians and Gynecologists Committee on Genetics, 2010). Hence, parents should be aware of the collateral information that may become available before making the decision about fragile X testing.

Even more serious ethical concerns, however, emerge in the context of predictive testing. Parents may seek to have their asymptomatic children tested for susceptibility to disorders that might appear later in life, invoking their right to know their children's vulnerabilities and to make family decisions (Tarini et al., 2009). They may have an interest in ensuring that they have some children free of the risk of developing a specific neuropsychiatric disorder and may seek testing as part of family planning. However, these interests come at the expense of the child to be tested. The results of the testing will provide no immediate benefit to the child and pre-empt the child's choice whether to be tested later in life. When a child is identified as being susceptible to a future disorder, parents may choose to allocate family resources for education and other opportunities in a way that is detrimental to the at-risk child. Moreover, parents may seek to protect at-risk children and alter their experiences in ways that can affect development or, perhaps more subtly, their self-images. Finally, test results may lead to discrimination in its many manifestations.

The Nuffield Council on Bioethics (1998) and other thoughtful commentators (Clark, 1994) have suggested that parents not be allowed to have their children tested for unpreventable adult-onset disorders; these decisions should be made by the children, once they reach adulthood. Parents should only be allowed to test when effective therapeutic interventions are available during childhood. The simplicity of this analysis, however, may be complicated by research on gene-environment interactions. Well-meaning parents may seek genetic testing with the intent to shield at-risk children from exposure to environmental circumstances that could interact with their genetic vulnerabilities to trigger neuropsychiatric disorders. Further developments in our understanding of gene-environment interactions and prophylactic interventions may unsettle the current ethical resolution of this issue.

Pharmacogenomic Profiling

Pharmacogenomic profiling refers to the study of genetic influences on drug responsiveness, including propensity for adverse reactions. Polymorphisms may lead to variable drug response by altering enzymatic metabolism or the sites of drug action. The promise of pharmacogenomics is that pharmaceutical drug development may be improved and clinicians enabled to personalize treatment based on individuals' genetic information. For example, identifying the genetic basis for treatment resistance could lead to the development of new therapeutic agents. Or, clinicians may be able use pharmacogenomic profiling to select specific medications that minimize the risk of adverse reactions and maximize the likelihood of treatment response (Wilke and Dolan, 2011).

In many instances, pharmacogenomic profiling raises few ethical concerns. But in some cases, the genetic markers used to profile drug response will convey other information that may be more problematic. For example, APOE profiles that provide information about risk of Alzheimer's disease may be helpful to internists in predicting treatment response to lipid-lowering statin medications (Nieminen et al., 2008). Thus, information that has been generated for pharmacogenomic purposes for the treatment of one condition conveys important risk information—that patients may not want to know—for another. At present, with genetic research progressing at a rapid pace, it is almost certain that some genetic information obtained in a context that appears to be low-risk will later be found to have more profound implications (Netzer and Biller-Andorno, 2004). During the informed

consent process, patients who are to undergo genetic testing *for any purpose* should understand that the results could later be found to have collateral implications.

Duties of Physicians to Patients' Families

Because genetic information may have significant consequences for patients' relatives, questions have been raised about whether physicians have a duty to warn family members when the results of genetic tests indicate they may be at risk. The courts in the United States have addressed this issue in a handful of cases that suggest what the appropriate ethical contours of such a duty might be.

In *Safer v. Pack* (1996), Ms. Safer sued Dr. Pack, her father's physician, who had treated him for ultimately fatal colon cancer due to familial adenomatous polyposis, which is usually an autosomal dominant disorder. Those with the disorder develop multiple benign polyps at a young age; progression to malignancy is inevitable unless the colon is removed. Dr. Pack had not told the family (Ms. Safer was 10 years old at the time of her father's death) about the underlying condition or its heritability, information known to the medical community at the time. Unaware of her risk, Ms. Safer took no precautions. At the age of 36 she was diagnosed with familial polyposis and metastatic carcinoma of the colon. The trial court dismissed her lawsuit, ruling that the absence of a doctor-patient relationship with Dr. Pack precluded recognition of a duty for the doctor to protect her. However, the New Jersey Superior Court reversed the lower court, holding that a physician had a "duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition." The duty to warn family members, as articulated in this case, would appear to trump patients' interest in confidentiality. The Florida Supreme Court, in *Pate v. Threlkell* (1995), articulated a narrower duty, one that did not sacrifice patients' right to privacy. Under *Pate*, which involved a claim brought by the family of a patient with medullary carcinoma of the thyroid, the physician must only warn the patient of the risk to family members, leaving it to the patient's discretion whether they are informed.

To date only one court has addressed information derived from genetic testing. In *Molloy v. Meier* (2004), the mother of a daughter with fragile X syndrome claimed that the child's physicians had failed to inform her about the risk of subsequently conceived children for mental retardation. The Minnesota Supreme Court held that "a physician's duty regarding genetic testing and diagnosis extends beyond the patient to biological parents who foreseeably may be harmed by a breach of that duty."

These cases suggest that courts are likely to find a duty to warn family members based on three factors: 1) the likelihood that family members are at risk, 2) the severity of the potential consequences, and 3) whether effective interventions exist to mitigate the risk. As previously discussed, genetic testing for neuropsychiatric disorders is likely to involve alleles that result in modest increase in relative risk (with the exception of autosomal dominant syndromes and highly-penetrant microdeletion and microduplication syndromes that carry higher risk, and for which testing may therefore be highly predictive). Psychiatric conditions generally are treatable, though neurodegenerative conditions are not, but in either case preventive measures are not currently available. Thus, at this point in time, it will usually be difficult to justify warning family members directly, particularly if this would involve a breach of patient confidentiality. However, it is good practice to advise patients of any increased risk to their family members, as this allows patients to decide whether and how to share information with them. The practice of providing information and placing responsibility in the hands of patients is supported by the public (Lehmann et al., 2000) and genetic counselors (Dugan et al., 2003) and may evolve into the standard of care.

Ethics in Genetic Research

Genetic research into neuropsychiatric disorders poses many of the ethical issues found in the clinic, from the challenge of explaining genetics clearly enough to laypeople to permit informed decisions about participation to concerns about discriminatory uses of genetic information uncovered in the research. But some issues peculiar to the research setting also arise, including whether consent must be obtained for subsequent use of deidentified samples in other research (Rothstein, 2010); community consultation or even consent should be obtained prior to research that may have implications for discrete population groups (Greely, 2001); participants' should be given access to their research data (Wolf et al., 2008); and investigators should be considered to have ongoing duties to subjects if subsequent analyses indicate risk of a disorder for which preventive interventions exist (Wolf et al., 2008). We lack the space here to consider even this truncated list of issues in detail, so we focus on the question of return of research data to subjects, which has attracted enormous interest.

In the early years of genetic research, when most findings were of uncertain clinical significance, investigators generally did not inform participants of their personal genetic results, which generally would have been of little use anyway. Today, however, with a growing number of loci associated with increased risk for the development of disorders—and in some cases clinical management--there is an evolving consensus among bioethicists that subjects who desire to receive genetic information should be given access to at least some of the findings (Bredenoord et al., 2011). Moreover, as whole genome and exome sequencing for research purposes become more common, the amount of data will skyrocket and the likelihood that some of it will be of interest to subjects will increase (McGuire et al., 2008).

In the most widely adopted formulation, return of research data is viewed as part of a reciprocal obligation of the researcher, in exchange for the subject's participation and trust (Richardson, 2008). Studies of subjects' preferences regarding access to information generated in genetic and genomic research have found consistent interest in knowing the results of these analyses, especially when actions can be taken to protect subjects' well-being or the well-being of their relatives (Murphy et al., 2008; Wendler and Emanuel, 2002). In keeping with these preferences, a growing number of federal agencies, expert panels, and authors have recommended that at least some genomic data be made available to subjects; although there are substantial differences in the specifics of these recommendations, there is general consensus that data should be offered when they have clear, actionable implications for subjects' health or behavior (e.g., Fabsitz et al., 2010; National Bioethics Advisory Commission, 1999; National Human Genome Research Institute, 2010).

Even with this consensus, however, it is inevitable that line-drawing problems will arise as emerging findings contribute to a shifting landscape of information. How substantial a risk and how effective an intervention must exist before disclosure is warranted (Biesecker and Peay, 2003; Wolf et al., 2008)? The fact that most of the associations of genetic loci with psychiatric disorders have not been subsequently confirmed provides sobering evidence of the difficulty of making these judgments. The time frame for verifying efficacy of some interventions may be very long and research designs may be prohibitively difficult. Consider the recent research findings that suggest the short allele for the serotonin transporter interacts with childhood stress to increase the risk of depression (Caspi et al., 2002). Does the instruction to parents to "help your child avoid stress" constitute an intervention? Must we await the findings of a controlled, longitudinal study before we can conclude that parents are justified in receiving this genetic information?

Moreover, there may well be reasons for disclosure even in the absence of prophylactic interventions. Couples may find information about carrier status to be valuable for reproductive planning. Persons at-risk for developing AD, for example, may use genetic information to make financial decisions, purchase insurance, or make other personal arrangements. As the earlier discussion of clinical testing suggests, a focus on medical interventions simply does not do full justice to individuals' concerns.

The final resolution of the problem of return of research data will be impacted by another set of issues, namely the burden on investigators to scan, interpret, confirm, and communicate results. To the extent that substantial resources are diverted from the research effort to this arguably collateral obligation, an argument can be made for significantly restricting its scope (Klitzman, 2006). Another important question relates to how meaningful informed consent for return of genomic data can be obtained from subjects when the extent and significance of potential findings are unknown. Final resolution may await results of studies soon to be under way to assess the costs and consequences of returning genomic data to human subjects.

Conclusion

Research on the genetics of neuropsychiatric disorders is unfolding a panorama of rich complexity. It is not yet possible to foresee the full ethical, legal, and social implications of the emerging data. However, genetic science promises to transform evaluation and treatment of neuropsychiatric disorders in ways that will continue to raise ethical concerns. In part, the extent of the ethical dilemmas will be driven by the predictive power of the science. Will complex, multi-gene and gene-environment interactions, along with epigenetic effects, diffuse and obscure the impact of the gene? Or will combinatory strategies be found to aggregate genetic susceptibilities and boost them toward new plateaus of insight?

The science will be revealed over time. But already it appears that genetics is headed out of the realm of research and into a wider base in the clinic. As genetic testing assumes its place in clinical practice, it is inevitable that a more diverse range of clinicians will find a broader set of applications for testing, and more innovative clinicians will be sought out by patients who are motivated to be "early adopters" of genetic testing. New questions and ethical concerns are likely to emerge in this fluid and uncertain era in neuropsychiatric genetics. The full involvement of the public in these issues will signal the maturation of the ethics of genetic science.

Acknowledgments

This work was supported in part by funding to Dr. Appelbaum from the National Human Genome Research Institute (1P20HG005535-01).

References

American Board of Genetic Counseling. 2011. http://www.abgc.net/ABGC/AmericanBoardofGeneticCounselors.asp

American College of Obstetricians and Gynecologists Committee on Genetics. ACOG Committee Opinion No. 469: Carrier screening for fragile X syndrome. Obstetrics and Gynecology. 2010; 116:1008–10. [PubMed: 20859177]

Appelbaum PS. Genetic discrimination in mental disorders: the impact of GINA. Psychiatric Services. 2010; 61:338–340. [PubMed: 20360270]

Arranz MJ, Kapur S. Pharmacogenetics in psychiatry: are we ready for widespread clinical use? Schizophrenia Bulletin. 2008; 34:1130–1144. [PubMed: 18753306]

Ashley EA, Gutte AJ, Wheeler MT, Chen R, et al. Clinical assessment incorporating a personal genome. The Lancet. 2010; 375:1525–1535.

Austin JC, Honer WG. The genomic era and serious mental illness: a potential application for psychiatric genetic counseling. Psychiatric Services. 2007; 58:254–61. [PubMed: 17287384]

Baars MJH, Henneman L, ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. Genetics in Medicine. 2005; 7:605–610. [PubMed: 16301861]

Bashford, A.; Levine, P. The Oxford Handbook of the History of Eugenics. New York: Oxford University Press; 2010.

Bassett AS, Chow EWC, AbdelMalik P, Gheorghiu M, et al. The schizophrenia phenotype in 22q11 deletion syndrome. American Journal of Psychiatry. 2003; 160:1580–1586. [PubMed: 12944331]

Bates BR, Lynch JA, Bevan JL, Condit CM. Warranted concerns, warranted outlooks: a focus group study of public understandings of genetic research. Social Science & Medicine. 2005; 60:331–344. [PubMed: 15522489]

Beach SRH, Brody GH, Gunter TD, Packer H, et al. Child maltreatment moderates the association of *MAOA* with symptoms of depression and antisocial personality disorder. Journal of Family Psychology. 2010; 24:12–20. [PubMed: 20175604]

Beauchamp, TL.; Childress, JF. Principles of Biomedical Ethics. New York: Oxford University Press; 2001.

Biesecker BB, Peay HL. Ethical issues in psychiatric genetics research: points to consider. Psychopharmacology (Berl). 2003; 171:27–35. [PubMed: 13680086]

Black, E. War Against the Weak: Eugenics and America's Campaign to Create a Master Race. New York: Dialog Press; 2008.

Bredenoord AL, Kroes HY, Cuppen E, Parker M, et al. Disclosure of individual genetic data to research participants: the debate reconsidered. Trends in Genetics. 2011; 27:41–47. [PubMed: 21190750]

Brosius J, Kreitman M. Eugenics—evolutionary nonsense? Nature Genetics. 2000; 25:253. [PubMed: 10888865]

Burke W, Pinsky LE, Press NA. Categorizing tests to identify their ethical, legal, and social implications. American Journal of Medical Genetics. 2001; 106:233–240. [PubMed: 11778984]

Caspi A, McClay J, Moffitt TE, Mill J, et al. Role of genotype in the cycle of violence in maltreated children. Science. 2002; 297:851–854. [PubMed: 12161658]

Caspi A, Sugden K, Moffitt TE, Taylor A, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003; 301:386–9. [PubMed: 12869766]

Clark, A. The Genetic Testing of Children: Report of a Working Party of the Clinical Genetics Society. London: Clinical Genetics Society; 1994.

Chiu RWKR, Zheng YWL, Leung TY, Sun H, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. British Medical Journal. 2011; 342:c7401.10.1136/bmj.c7401 [PubMed: 21224326]

Delisi LE, Bertisch H. A preliminary comparison of the hopes of researchers, clinicians, and families for the future ethical use of genetic findings on schizophrenia. American Journal of Medical Genetics, Part B Neuropsychiatric Genetics. 2006; 141B:110–115.

Dugan RB, Wiesner GL, Juengst ET, O'Riordan M, et al. Duty to warn at-risk relatives for genetic disease: genetic counselors' clinical experience. American Journal of Genetics, Part C Seminars in Medical Genetics. 2003; 119:27–34.

Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. American Journal of Psychiatry. 2011; 168:1041–1049. [PubMed: 21890791]

Fabsitz RR, McGuire A, Sharp RR, Puggal M, et al. Ethical and practical guidelines for reporting genetic research results to study participants. Circulation: Cardiovascular Genetics. 2010; 3:574–580. [PubMed: 21156933]

Faraone, SV.; Tsuang, MT.; Tsuang, DW. Genetics of Mental Disorders: A Guide for Students, Clinicians, and Researchers. New York: Guilford; 1999.

Finn CT, Smoller JW. Genetic counseling in psychiatry. Harvard Review of Psychiatry. 2006; 14:109–121. [PubMed: 16603476]

Finn CT, Wilcox MA, Korf BR, Blacker D, et al. Psychiatric genetics: a survey of psychiatrists' knowledge, opinions, and practice patterns. Journal of Clinical Psychiatry. 2005; 66:821–830. [PubMed: 16013896]

Galton, F. Inquiries into Human Faculty and its Development. London: Macmillan; 1883.

Garber KB, Visootsak J, Warran ST. Fragile X syndrome. European Journal of Human Genetics. 2008; 16:666–672. [PubMed: 18398441]

Goldman JS, Farmer JM, Van Deerlin VM, Wilhelmsen KC, et al. Frontotemporal dementia: genetics and genetic counseling dilemmas. The Neurologist. 2004; 10:227–234. [PubMed: 15335440]

Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, et al. ACMG Practice Guidelines: Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genetics in Medicine. 2011; 13:597–605. [PubMed: 21577118]

Gollust SE, Hull SC, Wilfond BS. Limitations of direct-to-consumer advertising for clinical genetic testing. JAMA. 2002; 288:1762–1767. [PubMed: 12365961]

Gollust SE, Wilfond BS, Hull SC. Direct-to-consumer sales of genetic services on the internet. Genetics in Medicine. 2003; 5:332–337. [PubMed: 12865763]

Greely HT. Informed consent and other ethical issues in human population genetics. Annual Review of Genetics. 2001; 35:785–800.

Greely HT. Get ready for the flood of fetal gene screening. Nature. 2011; 469:289–291. [PubMed: 21248817]

Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. Nature. 2011; 470:204–213. [PubMed: 21307933]

Green RC, Roberts S, Cupples LA, Relkin, et al. Disclosure of APOE genotype for risk of Alzheimer's Disease. New England Journal of Medicine. 2009; 361:245–254. [PubMed: 19605829]

Hassenfeld IN. Doctor-patient relationships in Nazi Germany and the fate of psychiatric patients. Psychiatric Quarterly. 2002; 73:183–194. [PubMed: 12143080]

Hodgkinson KA, Murphy J, O'Neill S, Brzustowicz L, et al. Genetic counseling for schizophrenia in the era of molecular genetics. Canadian Journal of Psychiatry. 2001; 46:123–130.

Hoop JG, Savla G, Roberts LW, Zisook S, Dunn LB. The current state of genetics training in psychiatric residency: views of 235 educators and trainees. Academic Psychiatry. 2010; 34:109–114. [PubMed: 20224019]

Hogarth S, Javitt G, Melzer D. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annual Review of Genomics and Human Genetics. 2008; 9:161–182.

Jamison, KR. Touched With Fire: Manic-Depressive Illness and the Artistic Temperament. New York: Free Press; 1993.

Jones I, Scourfield J, McCandless F, Craddock N. Attitudes towards future testing for bipolar disorder susceptibility genes: a preliminary investigation. Journal of Affective Disorders. 2002; 71:189–193. [PubMed: 12167515]

Karlsson JL. Psychosis and academic performance. British Journal of Psychiatry. 2004; 184:327–329. [PubMed: 15056577]

Kass, L. Life, Liberty, and the Defense of Dignity: The Challenge for Bioethics. New York: Encounter Books; 2004.

Kendler KS. "A gene for…" The nature of gene action in psychiatric disorders. American Journal of Psychiatry. 2006; 162:1243–1252. [PubMed: 15994704]

Kendler KS, Baker JH. Genetic influences on measures of the environment: a systematic review. Psychological Medicine. 2007; 37:615–626. [PubMed: 17176502]

Kim Y, Zerwas S, Trace SE, Sullivan PF. Schizophrenia genetics: where next? Schizophrenia Bulletin. 2011; 37:456–463. [PubMed: 21505112]

Klitzman R. Questions, complexities, and limitations in disclosing individual genetic results. American Journal of Bioethics. 2006; 6(6):34–36. [PubMed: 17085404]

Klitzman R. Exclusion of genetic information from the medical record: ethical and medical dilemmas. JAMA. 2010a; 304:1120–1121. [PubMed: 20823439]

Klitzman R. Misunderstandings concerning genetics among patients confronting genetic disease. Journal of Genetic Counseling. 2010b; 19:430–446. [PubMed: 20512408]

Klitzman R, Appelbaum PS, Chung W, Sauer MV. Anticipating issues related to increasing preimplantation genetic diagnosis use: a research agenda. Reproductive Biomedicine Online. 2008; 17(Suppl 1):33–42. http://www.rbmonline.com/Article/3517. [PubMed: 18644221]

Lawrence RE, Appelbaum PS. Genetic testing in psychiatry: a review of attitudes and beliefs. Psychiatry. In press.

Leehey M. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. Journal of Investigative Medicine. 2009; 57:830–836. [PubMed: 19574929]

Lehmann LS, Weeks JC, Klar N, Biener L, et al. Disclosure of familial genetic information: perceptions of the duty to inform. American Journal of Medicine. 2000; 109:705–711. [PubMed: 11137485]

Lo YM, Chan KC, Sun H, Chen EZ, et al. Maternal plasma DNA sequencing reveals the genome-wide genetic and mutational profile of the fetus. Science Translational Medicine. 2010; 2:61ra91.

Marteau TM, Croyle RT. The new genetics: psychological responses to genetic testing. British Medical Journal. 1998; 316:693–696. [PubMed: 9522800]

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature Neuroscience. 2009; 12:342–348.

McGuire AL, Caulfield T, Cho MK. Research ethics and the challenge of whole-genome sequencing. Nature Reviews Genetics. 2008; 9:152–156.

Meiser B, Kasparian NA, Mitchell PB, Strong K, et al. Attitudes to genetic testing in families with multiple cases of bipolar disorder. Genetic Testing. 2008; 12:233–244. [PubMed: 18554164]

Menasha JD, Schechter C, Willner J. Genetic testing: a physician's perspective. Mt Sinai Journal of Medicine. 2000; 67:144–151.

Meyer J-E. The fate of the mentally ill in Germany during the Third Reich. Psychological Medicine. 1988; 18:575–581. [PubMed: 3054989]

Miller DT, Adam MP, Aradhya S, Biesecker LG, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. American Journal of Human Genetics. 2010; 86:749–764. [PubMed: 20466091]

Milner KK, Collins EE, Connors GR, Petty EM. Attitudes of young adults to prenatal screening and genetic correction for human attributes and psychiatric conditions. American Journal of Medical Genetics. 1998; 76:111–119. [PubMed: 9511972]

Moldrup C. When pharmacogenomics goes public. New Genetics in Society. 2002; 21:29–37.

Molloy v. Meier. (2004). 679 N.W.2d 711.

Morrison PJ. Accurate prevalence and uptake testing for Huntington's disease. The Lancet Neurology. 2010; 9:1147.

Morrison PJ, Harding-Lester S, Bradley A. Uptake of Huntington disease predictive testing in a complete population. Clinical Genetics. 2010 published online Sept. 6. 10.1111/j. 1399-0004.2010.01538.x

Murphy KC. Schizophrenia and velo-cardio-facial syndrome. Lancet. 2002; 359:426–430. [PubMed: 11844533]

Murphy J, Scott J, Kaufman D, Geller G, et al. Public expectations for return of results from large-cohort genetic research. American Journal of Bioethics. 2008; 8:36–43. [PubMed: 19061108]

Munafo MR, Currant C, Lewis G, Flint J. Gene x environment interactions at the serotonin transporter locus. Biological Psychiatry. 2009; 65:211–219. [PubMed: 18691701]

National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Rockville, MD: 1999.

National Human Genome Research Institute. NHGRI Policy Recommendations on Research Privacy Guidelines. 2010. www.genome.gov/11510216

National Human Genome Research Institute. NHGRI funds return of results studies, forms expert consortium. 2011. http://www.genome.gov/27545526

Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. Bioethics. 2004; 18:344–360. [PubMed: 15449406]

Nieminen T, Kähönen M, Viiri LE, Grönroos P, et al. Pharmacogenetics of apolipoprotein E gene during lipid-lowering therapy: lipid levels and prevention of coronary heart disease. Pharmacogenomics. 2008; 9:1475–86. [PubMed: 18855536]

Nuffield Council on Bioethics. Mental Disorders and Genetics: The Ethical Context. West Sussex, UK: RPM Reprographics; 1998.

Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, et al. Genetic testing in the epilepsies—Report of the ILAE Genetics Commission. Epilepsia. 2010; 51:655–670. [PubMed: 20100225]

Pasche B, Absher D. Whole-genome sequencing a step closer to personalized medicine. JAMA. 2011; 305:1596–1597. [PubMed: 21505140]

Pate v. Threlkell. 661 So 2d 278 (Fla 1995)

Phelan J. Geneticization of deviant behavior and consequences for stigma: the case of mental illness. Journal of Health and Social Behavior. 2005; 46:307–322. [PubMed: 16433278]

Plomin R, Davis OS. The future of genetics in psychology and psychiatry: microarrays, genome-wide association, and non-coding RNA. Journal of Child Psychology and Psychiatry, and Allied Disciplines. 2009; 50:63–71.

Richardson HS. Incidental findings and ancillary-care obligations. Journal of Law, Medicine and Ethics. 2008; 36:256–270.

Richards M. Lay and professional knowledge of genetics and inheritance. Public Understanding of Science. 1996; 5:217–230.

Rothstein MA. Is deidentification sufficient to protect health privacy in research? American Journal of Bioethics. 2010; 10:3–11. [PubMed: 20818545]

Safer v Pack. (1996). 677 A.2d 1188

Smith LB, Sapers B, Reus VI, Freimer NB. Attitudes towards bipolar disorder and predictive genetic testing among patients and providers. Journal of Medical Ethics. 1996; 33:544–549.

Soliman A, Bagby RM, Wilson AA, Miler L, et al. Relationship of monoamine oxidase A binding to adaptive and maladaptive personality traits. Psychological Medicine. 2011; 41:1051–1060. [PubMed: 20810002]

Sullivan, J. State will admit sterilization past. Portland Oregonian; 2002 Nov 15.

Tam GWC, Redon R, Carter NP, Grant SGN. The role of DNA copy number variation in schizophrenia. Biological Psychiatry. 2009; 66:1005–1012. [PubMed: 19748074]

Tarini BA, Singer D, Clark SJ, Davis MM. Parents' interest in predictive genetic testing for their children when a disease has no treatment. Pediatrics. 2009; 124:e432.10.1542/peds.2008–2389 [PubMed: 19706561]

Thapar A, Harold G, Rice F, Langley K, et al. The contribution of gene–environment interaction to psychopathology. Development and Psychopathology. 2007; 19:989–1004. [PubMed: 17931430]

Torrey EF, Yolken R. Psychiatric genocide: Nazi attempts to eradicate schizophrenia. Schizophrenia Bulletin. 2010; 36:26–32. [PubMed: 19759092]

Trippitelli CL, Jamison KR, Folstein MF, Bartko JJ, et al. Pilot study on patients' and spouses' attitudes toward potential genetic testing for bipolar disorder. American Journal of Psychiatry. 1998; 155:899–904. [PubMed: 9659854]

United States Government Accountability Office. Direct-to-consumer genetic tests: misleading test results are further complicated by deceptive marketing and other questionable practices. GAO-10-847T. 2010 Jul 22. Available at: http://www.gao.gov/products/GAO-10-847T

United States Huntington's Disease Genetic Testing Group. Genetic testing for Huntington's disease: its relevance and implications (rev). Huntington's Disease Society of America; 2003. Available at: www.hdsa.org/images/content/1/1/11884.pdf

Vassos E, Collier DA, Holden S, Patch C, et al. Penetrance for copy number variants associated with schizophrenia. Human Molecular Genetics. 2010; 19:3477–3481. [PubMed: 20587603]

Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. The Lancet Neurology. 2011; 10:241–252.

Walsh T, McClellan JM, McCarthy SE, Addington AM, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008; 320:539–543. [PubMed: 18369103]

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, et al. Epigenetic programming by maternal behavior. Nature Neuroscience. 2004; 7:847–854.

Wendler D, Emanuel E. The debate over research on stored biological smaples: what do sources think? Archives of Internal Medicine. 2002; 162:1457–1462. [PubMed: 12090881]

Wilde A, Meiser B, Mitchell PB, Hadzi-Pavlovic, et al. Community interest in predictive genetic testing for susceptibility to major depressive disorder in a large national sample. Psychological Medicine. 2011; 41:1605–1613. [PubMed: 21159212]

Wilhelm K, Meiser B, Mitchell PB, Finch AW, et al. Issues concerning feedback about genetic testing and risk of depression. British Journal of Psychiatry. 2009; 194:404–410. [PubMed: 19407269]

Wilke RA, Dolan ME. Genetics and variable drug response. JAMA. 2011; 306:306–307. [PubMed: 21771992]

Winner JG, Goebert D, Matsu C, Mrazek DA. Training in psychiatric genomics during residency: a new challenge. Academic Psychiatry. 2010; 34:115–118. [PubMed: 20224020]

Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, et al. Managing incidental findings in human subjects research: analysis and recommendations. Journal of Law, Medicine and Ethics. 2008; 36:219–248.