GENETIC TESTING FOR AUTISM PREDISPOSITION: ETHICAL, LEGAL AND SOCIAL CHALLENGES

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I. INTRODUCTION

Over the past two decades, it has become increasingly clear that many of the most important diseases affecting the population of industrialized nations—including cancer, heart disease, diabetes, and various neurological impairments—have complex etiologies that involve multiple genetic and environmental factors interacting in complex ways to produce disease phenotypes. While these developmental interactions are difficult to study, the scientific investigation of such conditions is further complicated by the likelihood of heterogeneity within previously simple disease categories in terms of causes, symptoms, and outcomes. The complexity of these important diseases and their development not only presents challenges to scientists trying to improve the understanding, diagnosis, treatment, and prevention of such diseases, but it also raises more complex ethical, legal, and social issues (ELSI). There may be no better example to explore the ELSI associated with complex diseases than autism (now also known as the Autism Spectrum Disorders or ASD), a neurobiological and behavioral syndrome that includes multiple subtypes.

Several features of autism make it a useful case study for in-depth exploration of the range of ELSI involved in the research and application of genetic markers of a complex disease, including:

- Autism is a major population health priority, with the incidence of the disease now reported at 1 in 150 U.S. births;¹
- While autism appears to be caused by a combination of genetic and environmental factors, there is a strong and unambiguous genetic component that may explain as

much as 80-90% of the risk for autism;²

- There does not appear to be one primary genetic allele that causes autism, but rather there are likely to be a number of different genetic variants that increase the risk of autism;³
- Autism is not a single, uniform disease, but rather appears to consist of a spectrum of diseases with a range of severity and symptoms, and possibly, different etiologies and natural histories;⁴
- There are some limited treatment options for autism, but such treatments are most beneficial when commenced early, perhaps even prior to clinical diagnosis, thus creating the potential for beneficial uses of autism genetic markers;
- Because it is a disease that generally strikes children, it raises additional and complex ethical and social issues in the realm of pediatrics and pediatric research;
- Autism triggers strong emotional responses and political activism due to the tragic and apparently growing impacts of the disease and the controversies over its etiology, including the role that genetics and various environmental factors play; and
- Relatively little published research has been undertaken on the ELSI associated with autism genetics to date.

This article seeks to identify and discuss the ethical, legal and social implications of the role and use of genetics with respect to autism. It first summarizes autism and recent scientific findings about genetic factors in autism (Part II). After briefly discussing the controversy over any role for genetics (Part III), it goes on to analyze various potential applications of genetics in the diagnosis,

classification, and treatment of autism, and the ELSI raised by each potential application (Part IV).

II. BRIEF OVERVIEW OF AUTISM AND AUTISM GENETICS

A. Autism Diagnosis and Treatment

Autism is a pervasive developmental disorder (“PDD”) with a childhood onset characterized by abnormalities in (1) social interaction, (2) language, communication, and imaginative play, and (3) range of interests and activities.5 The prevalence of autism is currently about 1 in 150 children.6 Four times as many boys as girls are afflicted with autism.7 Every year new diagnoses will cost the United States $35 billion over the patients’ lifetimes.8 The prevalence and impacts of autism make this condition a major health and economic priority for the nation, as well as a difficult challenge, and in extreme cases tragedy, for many individual families.

As discussed further below, the issue of whether the incidence of autism has increased over time is a very important and controversial question, as an increase over time would be consistent with an environmental cause.9 Over the past 30 years, the recorded incidence of autism diagnoses has increased from approximately one in 2500 to the current estimate of one in 150.10 This increase in detection could represent a true increase in the incidence of the disease, or it could simply be an artifact of better or evolving diagnostic measures. Some experts adhere to the latter view, attributing the increased frequency

6 Rice, supra note 1, at 12.
7 Eric Fombonne, Epidemiology of Autistic Disorder and Other Pervasive Developmental Disorders, 66 J. CLINICAL PSYCHIATRY (Suppl.10) 3, 5 (2005).
10 Rice, supra note 1, at 12.
of diagnosis to secondary factors such as “changes in diagnostic practice associated with more trained diagnosticians; broadening of diagnostic criteria to include a spectrum of disorder; a greater willingness by parents and educationalists to accept the label (in part because of entitlement to services); and better recording systems, among other factors.” 11 This issue is of more than passing scientific interest, because in the words of one group of skeptics of an autism “epidemic,” “[e]pidemics solicit causes; false epidemics solicit false causes.” 12

Others take a different view and believe that the rate of autism is truly increasing, often describing the situation as an “epidemic.” Such a view is consistent with the view that changes in our environment are the primary cause of autism since genetic changes, which occur slowly over centuries or even millennia, do not occur fast enough to explain the rapid increase in autism diagnoses observed in recent decades. 13 A recent study in California is cited in support of this view. The study found that autism rates have increased 500-600 percent in children born in California since 1991. Factors such as younger age at diagnosis, the inclusion of milder cases within the category of ASD, and differential migration of families with autistic children to California, combined, could only explain a 68 percent increase in autism diagnosis, or about 10 percent of the total recorded increase. 14 The published report of the study itself was quite restrained in interpreting the results, noting that “[o]ther artifacts have yet to be quantified, and as a result, the extent to which the continued rise represents a true increase in the occurrence of autism remains unclear.” 15 In a press release


12 Gernsbacher et al, supra note 11, at 58.

13 Blaxill, supra note 9, at 537.


15 Id.
accompanying the publication of the report, however, the lead author was less restrained, stating that the study results suggest “[i]t’s time to start looking for the environmental culprits responsible for the remarkable increase in the rate of autism in California.”

In addition to the increase in diagnostic frequency (whether it represents a true increase or an artifact of better surveillance or changes in diagnostic criteria), another important aspect for understanding autism is that it is a heterogeneous condition with a substantial range in severity and symptoms. There is no laboratory test to detect autism; rather diagnosis is based solely on behavioral characteristics. There are now five recognized autism subtypes with the broader term “Autism Spectrum Disorders” that include: (1) autistic disorder; (2) Asperger’s disorder; (3) Pervasive Developmental Disorders Not Otherwise Specified (“PDD NOS”); (4) disintegrative disorder; and (5) Rett disorder, with the first three subtypes being most commonly associated with ASD. Notwithstanding this categorization, ASD likely involves a continuum along a spectrum rather than one or more discrete diseases, as substantial variation exists both between and within these subtypes of the condition.

Some individuals with autism function nearly “normally” in society, including such extraordinary talented and successful people such as Isaac Newton and Andy Warhol. Others have more severe conditions, ranging from moderate behavioral problems to severe dysfunction, including substantial cognitive impairment. As described by one recent study, the manifestations of the ASDs “range from a nonverbal child with severe mental retardation and self-injury to a high-functioning


17 Zoran Brkanac, et al., Pharmacology and Genetics of Autism: Implications for Diagnosis and Treatment, 5 PERSONALIZED MED. 599, 599 (2008). Autism disorder is characterized by deficits in communication, social interaction and repetitiveness; Asperger’s disorder is characterized by the lack of communication and intellectual impairments; and PDD NOS is diagnoses for children with autism syndromes that do not meet the criteria for autistic disorder or Asperger’s disorder. Id.

college student with an above-average IQ despite impaired language use and inadequate social skills.”

Because of the range of symptoms and severity, as well as the heterogeneity of the condition, autism is sometimes difficult to diagnose. Current screening measures are typically based on behavioral data (e.g., developmental questionnaires, attaining appropriate developmental milestones, clinician observation, parental reports). Although it has been shown that these tools are capable of identifying behaviors that distinguish healthy infants from infants with autism by 18 months of age (e.g., eye contact, joint attention, pretend play, language development), these screening methods may not be sufficiently sensitive for diagnosis of individuals with milder autistic spectrum disorders, such as high-functioning autism or Asperger’s disorder. This lack of sensitivity is due in part, no doubt, to the difficulty of accurately diagnosing autism: and that less than 30 percent of primary care providers conduct standardized screening tests as a matter of practice.

A report by the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society regarding the screening and diagnosis of autism noted a survey of 1300 families that revealed an average age at diagnosis of about six years in spite of the fact that many parents had concerns by the time their children were 18 months of age. At the time of initial presentation, fewer than 10% of these children were accurately diagnosed with autism. Another 10% were not diagnosed and no further actions were taken; the remainder was referred to a

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20 Id.
22 Filipek et al., supra note 22, at 469.
23 Id.
specialist. Of those referred, only 40% were given a formal diagnosis and 25% were again referred. Typically, the definitive diagnosis of autism is not made until several years after parents notice the symptoms, and anecdotal reports indicate large variations in age of diagnosis as a function of the quality of clinical resources available to families.

The delay and difficulty in diagnosing autism is particularly concerning given that intensive treatment initiated early in the course of the disease has been shown to result in improved outcomes for many children. The benefits of early treatment have been demonstrated in a variety of studies, and the research suggests that intervention prior to three or three and a half years of age has the greatest benefit. Currently, the gold standard of treatment is early intensive behavioral intervention using techniques of Applied Behavioral Analysis (ABA). However, this treatment, even when started early, is not successful for all affected children, and according to a recent review, “[t]here is an urgent need for more efficacious pharmacologic and cognitive-behavioral therapies and a better notion of which therapy is most appropriate for which child.” A variety of other treatments, including pharmacological treatments, are currently being investigated for “possible use in” early intervention.

Early treatment results not only in better outcomes, but also appears to produce more lasting benefits. The reasons proffered include the decrease in brain plasticity as children age, as well as the increased difficulty in changing negative and pathological behaviors

24 Id.
25 Id.
26 Id.; see also RAUN D. MELMED, AUTISM EARLY INTERVENTION 39-66 (2007).
29 Geschwind, supra note 2, at 375.
as children age.\textsuperscript{31} The temporally-sensitive benefits of early treatment and the pervasive and refractory nature of the disease make it increasingly important that intervention, and consequently diagnosis, take place as early as possible.\textsuperscript{32}

B. Causes and Genetics of Autism

The cause of autism has not been determined, but the majority of autism cases are likely the result of an interaction between multiple genes and environmental factors during development, including prenatal development.\textsuperscript{33} A variety of environmental (e.g., prenatal or postnatal exposures to toxins, hormones, or teratogens; prenatal infections; vaccines) and demographic (e.g., parental age) factors have been hypothesized as causes of autism, but the available data has not clearly defined which of these types of factors play a significant role in autism causation (discussed further in Part III).\textsuperscript{34} In recent years, the evidence supporting a genetic role in autism has been expanding, and many researchers now describe autism as one of the most heritable brain disorders, even if not literally inherited.\textsuperscript{35} Estimates of the heritability of autism (i.e., the proportion of variation within the population that is explained by genetic factors) are as high as 90 percent.\textsuperscript{36}

The initial evidence of a strong genetic basis for autism came from family history studies. For example, the risk of developing autism if a sibling has been diagnosed with ASD is between two and eight percent, which is at least 25-fold higher than the prevalence in

\textsuperscript{31} Butter et al., \textit{supra} note 29, at 677-680.

\textsuperscript{32} Butter et al., \textit{supra} note 29, at 677-678.

\textsuperscript{33} See \textit{NATIONAL ACADEMY OF SCIENCES, IMMUNIZATION SAFETY REVIEW: VACCINES AND AUTISM} \textit{9} (May 2004); Muhle et al., \textit{supra} note 19, at e473; S.J. Spence, \textit{The Genetics of Autism}, 11 \textit{SEMINARS PEDIATRIC NEUROLOGY} 196, 196 (2004).

\textsuperscript{34} Muhle et al., \textit{supra} note 19, at e473.

\textsuperscript{35} Brian J. O’Roak & Matthew W. State, \textit{Autism Genetics: Strategies, Challenges and Opportunities}, 1 \textit{AUTISM RESEARCH} 4, 4 (2008) (“Autism is generally accepted as the most genetic of all developmental neuropsychiatric syndromes”); Gupta & State, \textit{supra} note 3, at 429; Brkanac et al., \textit{supra} note 17, at 600.

\textsuperscript{36} Geschwind, \textit{supra} note 2, at 372.
the general population. Also, siblings and parents of children diagnosed with autism are more likely to exhibit signs (sub-threshold traits) associated with autism, and mild autistic traits appear in many first-degree relatives of a family member diagnosed with ASD. Twin studies show that concordance rates for monozygotic twins are higher than those for dizygotic twins. For instance, one study examined 27 pairs of monozygotic (MZ) twins and 20 dizygotic (DZ) twins and found 60 percent of MZ pairs were concordant for autism versus 0 percent of DZ pairs. When the researchers looked at the broader phenotype of social and communication deficits, 92% of MZ twins were concordant compared to 10% of DZ pairs.

In a small percentage of autism cases, the condition appears to be critically dependent on a single gene or genetic abnormality. Approximately 10 percent of autism cases are estimated to be caused by defined mutations or genetic syndromes (e.g. tuberous sclerosis complex, fragile X syndrome). For example, Fragile X syndrome, caused by mutations in the fragile X mental retardation 1 (“FMR1”) gene, is the most common genetic cause of intellectual disability in the U.S. and is also the most common single gene associated with autism to date. Approximately 15 to 35 percent of individuals diagnosed with Fragile X syndrome (depending on method used for diagnosis) are also diagnosed with autism, which represents approximately two percent of all autism cases. Mutations in the X-linked methyl-CpG-binding protein 2 (“MECP2”) gene have been identified as the cause in some cases of Rett syndrome, a type of autism that primarily affects females.
In most cases of ASD without a specific single genetic cause, which are often referred to as “idiopathic” or “primary” ASD, genetic factors also appear to play a major (but not exclusive) role in disease causation. Genetic association studies have recently started identifying specific genetic markers associated with a susceptibility to autism, although identification of the genetic factors which cause or increase the risk of autism remain elusive, due in part to the substantial variability in expression and the likely etiological heterogeneity of the disease. This is a common predicament in neuropsychiatric and neurobiological research. Estimates of the number of genetic loci contributing to autism risk range from 10 to over 100 different genes.

A variety of cytogenetic changes have been associated with increased risk of autism, including deletions in chromosomal regions 7q, 22q13, 2q37, 18q, and Xp, as have sex chromosome aneuploidies (XYY and XO/XY mosaicism). Estimates in recent studies indicate that de novo copy number variations (“CNVs”) may be involved in 10-40% of cases of autism. These CNVs involve micro duplications,

45 Muhle et al., supra note 19, at e475; Lintas & Persico, supra note 18, at 2.
46 Gupta & State, supra note 3, at 429; Brkanac et al., supra note 17, at 600. One recent review summarized the frustration of many researchers about the difficulty of unraveling the genetic basis of autism as follows:

"While the rationale for placing an emphasis on DNA is well justified and the goals of the work laudable, it is fair to say that the record of achievement with regard to gene discovery has not been all that scientists, patients or family members might have hoped for. The road has been long, difficult and at times extremely frustrating, characterized by tantalizing leads that have been difficult to confirm . . . ."

O’Roak & State, supra note 35, at 4.
48 Gail E. Herman et al., Genetic Testing in Autism: How Much Is Enough?, 9 GENETICS IN MEDICINE 268, 268 (2007); Brkanac et al., supra note 17, at 600; Muhle, et al., supra note 19, at e475.
49 Muhle et al., supra note 19, at e476-78; M.-L. Jacquemont et al., Array-based Comparative Genomic Hybridisation Identifies High Frequency of Cryptic Chromosomal Rearrangements in Patients with Syndromic Autism Spectrum Disorders, 43 J. MED. GENETICS 843, 843 (2006).
50 Jacquemont et al., supra note 50, at 847; J. Sebat et al., Strong Association of De Novo Copy Number Mutations with Autism, 316 SCIENCE 445, 445 (2007); O’Roak & State, supra note 35, at
deletions or other rearrangements of the chromosome that result in increased or decreased copies of a particular genetic sequence, and may either occur spontaneously or by inducement of by some environmental or other factor. In addition to their scientific value, the nature of these changes have social significance because although they are "genetic" they are not always inherited from the father or mother, but rather often arise de novo during reproduction. This could affect both parental perceptions of responsibility and the risk of autism in future children of parents with a child with ASD attributed to a de novo CNV.

A variety of individual genes have also been identified as candidates involved in autism predisposition. For example, mutations in the Neuroligin 4 (NLGN4) gene have been associated with autism in a number of studies. Mutations in the PTEN gene, one of the protein tyrosine phosphatase genes which are implicated in a family of rare tumor syndromes, have also been identified at a fairly high rate in children with autism. One study found that 17% of the patients with macrocephaly and autism had PTEN mutations. Several studies have recently reported an association between mutations in the Contactin Associated Protein-Like 2 ("CNTNAP2") gene. Other individual genetic loci that appear to confer susceptibility to ASD have recently been identified.

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52 See, e.g., J. Yan et al., Analysis of the Neuroligin 4Y Gene in Patients with Autism, 18 PSYCHIATRIC GENETICS 204 (2008). See generally Brkanac et al., supra note 17, at 601 (reviewing other studies).


56 See Lintas & Persico, supra note 18, at 2-5; Brett S. Abrahams & Daniel H. Geschwind, Advances in Autism Genetics: On the Threshold of a New Neurobiology, 9 NATURE REV. GENETICS...
generically caused metabolic disorders, such as phenylketonuria and some mitochondrial disorders, have also been associated with autism.\footnote{Muhle et al., supra note 19, at 475.}

Notwithstanding the slow and, at times, frustrating progress in characterizing the genetic factors contributing to autism, many scientific experts in the field are optimistic that clinically useful genetic markers of autism have been, or will soon be, identified as a result of new genetic technologies and increased funding of research.\footnote{O’Roak & State, supra note 35, at 4. (stating “even the most skeptical observer cannot help but be optimistic about the future of this area of research”); Gupta & State, supra note 3, at 435.}

Identification of the mutations, polymorphisms, or other genetic variants that predispose one to autism would provide an ‘at-risk’ diagnostic and allow DNA-based testing for autism susceptibility at the earliest points of life. Some of these applications and the associated issues are discussed in part IV after further exploration concerning the controversy over the causes of autism and the role that genetics may play.

III. GENETICS AND THE CONTROVERSY OVER AUTISM CAUSATION

The question of what causes autism has moved beyond the biomedical research and clinical practice communities and has developed into a highly charged, emotional debate involving scientists, physicians, journalists, families of children diagnosed with ASD, and disease advocacy groups. At one time, media and popular reports tended to implicate bad parenting (e.g., “refrigerator mothers” with cold emotional support for their children) as a cause or contributor, but those theories have now been refuted and it is widely accepted that there is a biomedical origin of the condition.\footnote{Geschwind, supra note 2, at 368; Abrahams & Geschwind, supra note 56, at 341.} Nevertheless, the historical residue of this tendency to “blame the parents” no doubt contributes to some of the current sensitivities and political controversy surrounding the issue of autism causation.
The increase in autism diagnosis over the past few decades has stirred fears that there may be an environmental factor that is responsible. Families of many children with autism are understandably anxious to identify any such factor, both to explain the mystery of their child’s condition, and to prevent similar impacts on future children. Many suspected environmental causes of autism have been fingered, including mercury in the environment, childhood vaccines (including the mercury preservative thimerosal used in some vaccines), other pollutants, prenatal stress, ultrasounds, the level of precipitation in an area, and even television.60 Demographic factors such as parental age and birth order have also been identified as potential contributing causes.61

No greater controversy exists in the autism field than the issue of whether childhood vaccines, or the thimerosal preservative used in some vaccines, causes autism. Propelled by a now discredited Lancet article62 and the crusades of several celebrities such as Jenny McCarthy and Jim Carrey, an advocacy movement powered mostly by autism family support groups has emerged to argue that childhood vaccines cause autism.63 This claim regarding the topic of autism is disputed by most scientists and leading scientific organizations, including the National Academy of Science’s Institute of Medicine, based on a series of large studies that have found no association between autism and childhood vaccines generally, or thimerosal specifically.64 In addition, some of the larger autism


64 E.g., INSTITUTE OF MEDICINE, IMMUNIZATION SAFETY REVIEW: VACCINES AND AUTISM (2004); Richard Reading, Thimerosal and the Occurrence of Autism: Negative Ecological Evidence from
support groups have sided with scientists in contesting the claim that vaccines cause autism, which they view as a diversion that is siphoning resources and attention away from more valuable types of autism research. This disagreement has led to a highly polarized schism in the autism community between the vaccine opponents and the mainstream scientific community.65

It is in this contrary environment that recent findings of a genetic association with autism have been published, leading to an expected backlash by vaccine opponents.66 These groups see any attempt to explain autism by genetics as both a personal attack on the parents (and their genes), implying that they are as responsible for their children’s autism, and as a deliberate effort by scientists to divert attention from environmental causes of autism, such as vaccines.67 Recent findings that a significant portion of the “genetic” contribution to autism consists of de novo copy number mutations may help address some of these concerns.68


68 Refer to notes 51-52 supra and accompanying text.
Notwithstanding the heated emotion over the role of genetics in autism, this debate, like the larger “nature versus nurture” debate in which it is nested, is largely a false controversy.69 Autism, like most complex diseases, is likely caused by the interaction of genetic and environmental factors.70 The discovery of genetic predispositions to autism does not, therefore, preclude co-existing environmental causes. This is particularly true if, as some believe,71 the true rate of autism in the population is increasing; in which case some type of combination of environmental or behavioral changes in society must be responsible for the increased incidence.

Population gene frequencies have not changed significantly enough over the past two to three decades to explain the increase in autism rates on their own. However, the fact that there may be environmental factors contributing to autism does not justify ignoring or rejecting the findings of genetic associations. In fact, the genetic data may help identify and elucidate environmental factors, as it is quite likely that autism results from the association between certain environmental factors and specific predisposing genetic variants.72 While the role of environmental factors may be hidden in population-wide studies, the association becomes clear when the population is divided by genetic subtype which can provide the higher resolution needed to observe specific associations between environmental factors and autism in certain genetic subtypes.73 As one expert recently explained, “[a] more thorough understanding of the genetic factors, which compose a significantly larger proportion of ASD risk than environmental factors, will facilitate identification of environmental contributions by suggesting mechanisms and

70 Lintas & Persico, supra note 18, at 1.
71 Refer to text accompanying notes 14-17 supra.
providing more homogeneous etiological subtypes in which to examine gene-environment interactions.”74 Nevertheless, any discussion of the ELSI associated with autism genetic markers must be cognizant of the heated social environment in which such issues will arise and be addressed.

IV. ETHICAL, LEGAL AND SOCIAL ISSUES RELATING TO THE USE OF AUTISM GENETIC MARKERS

The putative identification of pre-symptomatic genetic markers of susceptibility to autism raises a series of ethical, legal and social issues. There are numerous potential ways that genetic information may be used for autism research, classification, diagnosis, screening, treatment, prevention, and litigation. These potential applications of autism genetic markers, and the Ethical, Legal and Social Issues (ELSI) they are likely to present, are addressed below.

A. Genetic Research Regarding Autism

Genetic variants that have been associated with autism susceptibility can be used in genetic epidemiology studies to better understand potential environmental, demographic, and behavioral factors that may affect autism development and risk. Like many complex diseases, autism appears to result from an interaction of environmental and genetic factors.75 It is likely that some environmental factors are most likely to affect individuals with certain genetic predispositions, which has been observed for many other environmental exposures.76 In such gene-environment studies, the exposed population would be stratified by genotype with respect to the potential genetic markers of autism in order to look for associations that may not be detectable if looking at the entire population. This approach will provide a much higher resolution

74 Geschwind, supra note 2, at 370.
75 Lintas & Perisco, supra note 19, at 1.
approach for identifying potential environmental causes of autism.\textsuperscript{77}

Such gene-environment studies will raise a number of ELSI. All genetic testing of children for autism traits will require informed consent from their parents. The informed consent process will be complicated by the complex nature of autism and the non-deterministic nature of any genetic predispositions to autism.\textsuperscript{78} People often misunderstand the implications of their genetic data, believing that a genetic predisposition necessarily results in the development of their illness.\textsuperscript{79} Given the potential problem of poor comprehension of the relevant information, how should informed consent be obtained? What type of information should be included, and how should the relevant information be communicated?

A related concern is whether research subjects (or their parents) will be informed of which autism predisposition alleles they carry. Because the risks associated with such alleles may not have been validated yet, or may involve risks which cannot be reduced, some researchers in other contexts (e.g., Alzheimer’s research) have been reluctant to disclose genetic test results to research subjects because of the lack of any benefits from such knowledge and the existence of potential risks in terms of psychological stress, potential for misunderstanding, and possible misuse of the information by third parties (e.g., insurers or employers).\textsuperscript{80} On the other hand, from an autonomy perspective, it could be argued that subjects should be entitled to receive their genetic information if they so desire. Whether there is a moral obligation to return research results to research subjects remains a hotly contested issue in the ethics literature.\textsuperscript{81} This issue will need to be addressed in the informed consent process for the research subjects.


\textsuperscript{80} McMahon, et al., \textit{supra} note 79, at 56.

\textsuperscript{81} Fiona A. Miller et al., \textit{Duty to Disclose What? Querying the Putative Obligation to Return Research Results to Participants}, 34 J. MED. ETHICS 210, 210 (2008).
Another issue of relevance regarding informed consent to genetic research on complex disorders, including studies of gene-environment interactions, is the scientific desirability, but ethical quagmire, of consent to future use of genetic samples and associated environmental data, whether de-identified or not. A final informed consent issue frequently arising in autism research lies in the responsibilities to family members of research subjects with autism, who are often directly or indirectly implicated in the research and its findings.

B. Genetics and the Diagnosis of Autism

Accurate and timely diagnosis is critical for addressing autism in clinical settings. Establishing a diagnosis and understanding the underlying etiology may aid in predicting the prognosis, determining accurate recurrence risk, starting appropriate treatment and health maintenance planning, and offering family members considerable emotional relief. Children exhibiting symptoms or characteristics of autism might be genetically tested for autism predisposition genes to assist in diagnosing autism early in its development. The threshold question for this application is: how will the identification of a genetic marker in a child assist in the diagnosis or treatment of that child’s condition? For example, will there be different treatment options based on the results of genetic testing? If not, will there be any other benefits for the child from identifying a genetic contributing cause? Will there be any benefits to the parents in terms of planning for future children? What are the risks that such testing might entail (e.g., in terms of parent-child relations, child’s own self-

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83 Donna T. Chen et al., *Ethical Aspects of Research Into the Etiology of Autism*, 9 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RESEARCH REV. 48, 48-52 (2003); McMahon et al., *supra* note, 79 at 56.


85 Brkanac et al., *supra* note 17, at 604 (“With identification of an increasing number of genes that are involved in autism, molecular genetic evaluation will become increasingly more important as a standard screening tool together with behavioral assessment.”); McMahon et al., *supra* note 79, at 53.
image, and insurability)? How well characterized and validated must the genetic test be before it can be used for such purposes?

It is also important to understand how individuals perceive the genetic risk of their child developing autism given that genetic testing for complex diseases such as autism provides only the probability of developing the disease. It is unlikely that there will be a bright line between disease and non-disease status in people exhibiting autism traits, so how will genetic markers contribute to delineation of disease status from non-disease status? It has been shown that, regarding results from genetic testing, individuals often interpret probabilities as either presence or absence of the disease. The fact that mutations or polymorphisms are reported as either present or not present (despite the fact that the risk of developing the disease is probabilistic) may further exacerbate the problem. Knowledge that a young child and possibly other family members carry a genetic predisposition to autism may create a whole series of stigmas and negative perceptions related to being “at risk.”

There is some evidence associated with other genetically influenced diseases that the existence of a genetic explanation for a child’s disease can provide emotional relief for the parents. However, a parent who is found to have contributed the genetic marker to an autistic child may have feelings of guilt and responsibility. Siblings of an individual with autism who are found to carry the same genetic marker but who did not develop autism may have misgivings and anxieties about becoming a parent and passing on such a trait to their children.

Another issue in using genetic tests in the autism diagnosis process will be the availability of reimbursement for autism genetic testing by third party payers such as Medicare/Medicaid and private

89 McMahon et al., supra note 79, at 54.
Genetic testing for complex genetic diseases such as autism presents a new set of challenges for third party payers. For example, what probability of developing autism must a genetic marker predict before an insurer will agree to pay for the test? Due to high resolution in a “tiered” neurogenetic approach, this method may be met with a high level of acceptance from third-party payers. What percentage of children identified as carrying the predisposition gene will benefit from pre-symptomatic genetic testing? Will genetic testing of symptomatic children diagnosed with autism provide for better outcomes via better targeted therapies? What criteria will governmental and private third party payers use to make these determinations?

Another set of ELSI relating to the potential use of autism genetic markers for diagnosing autism involve how the testing is conducted, including by whom and of whom. Obviously, testing by a physician after consultation and consent of the family will be the primary testing context, but other contexts that may be more problematic are also possible. For example, what if third parties such as a school or counselor want to conduct such testing as part of the evaluation of a child experiencing problems? There are potential benefits associated with such uses, but also many potential risks in terms of misunderstanding and misuse of the test results.

Another issue is whether (and should) the genetic tests will be made available to consumers directly over the internet (“direct to consumer” or DTC testing) for families who want to conduct such tests privately without the participation of their physician. In other words, should genetic testing for autism be part of a suite of clinical services, or should it be offered directly to worried parents? Although no company currently offers autism genetic predisposition tests direct-to-consumer, this may change in the near future if demand develops. One problem already encountered with current

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91 Schaefer & Lutz, supra note 2, at 553.
DTC genetic tests is that the significance of the specific genetic tests that some of the companies are currently offering is over-stated, because the clinical validity and utility of the tests being offered have not been validated. In addition, DTC offers no opportunities for appropriate counseling from healthcare professionals and may result in consumer confusion regarding the genetic information provided.

C. Genetics and Disease Classification

One important application of genetic markers for autism is likely to be in classifying disease subtypes. Autism is a heterogeneous disease that involves a spectrum of conditions and effects ranging from severe to mild. As discussed above, five different subtypes of autism have already been delineated. It is possible that genetic markers may lead to the inclusion of more disorders within the Autism Spectrum of Disorders, or that they may be helpful in distinguishing additional subclasses of disease with different treatment and outcomes, whereby genetic data will help further split up the diagnostic categories. Already, genetic discoveries are largely responsible for “[t]he emerging notion of ASD as ‘the autisms,’ a collection of dozens or perhaps hundreds of etiological forms that converge on common behavioral or cognitive phenotypes.”

This classification of disease subtypes using genetics or other biomarkers raises issues such as how this use of autism genetic markers will be integrated into clinical care. Will diagnosis of autism vary by autism genotype? Will doctors recommend different treatments to autism patients based on which gene variants they carry? Will health insurers agree to cover different treatment options

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94 Refer to note 18 supra and accompanying text.

95 Geschwind, supra note 2, at 372.

based on the patient’s genotype?

Before any autism genetic markers could be used for such clinical applications, the markers will need to be adequately validated. In particular, the analytical and clinical validity and utility of any autism genetic marker will be critical to its clinical utilization.97 How will such tests be used by healthcare professionals and families if, as seems likely, such tests are commercialized with limited clinical utility and prior to any proven treatment regimen based on the test results?98 The American College of Medical Geneticists has recently published guidelines to assist physicians in considering these issues in deciding whether and how to genetically test their patients suspected or diagnosed as having autism.99

There is a related set of issues concerning the likelihood that multiple genetic alleles will be found to play a role in autism predisposition. How will the information from the various genetic variants be integrated or coordinated? Will all relevant genetic variants be offered by a single diagnostic test product, or will doctors and their patients need to use a selection of tests owned by different patent-holders and product developers? How will decisions be made about which genetic variants should or should not be included in a testing battery for purposes of classifying autism subtypes?

D. Using Genetics to Tailor Autism Treatment and Therapy

Another potential application of autism predisposition genes is to use these genetic differences to target treatments and therapies. The developing paradigm of personalized medicine seeks to individualize therapy based on the patient’s molecular profile on the assumption that molecular markers can be used to differentiate and classify different subtypes of the disease or to target variation in pharmacokinetics that affect drug metabolism. A classic example is targeting the breast cancer drug herceptin to patients with tumors

97 See generally W. Burke & R. Zimmerman, Ensuring the Appropriate Use of Genetic Tests, 5 NATURE REV. GENETICS 955 (2004); McMahon et al., supra note 79, at 53-54.
98 McMahon et al., supra note 79, at 54.
that express the HER protein on their cell surface (“HER+”), based on data showing that the drug was only effective against such tumors.

While no such treatment-specific associations have been validated for autism genetic markers to date, it is possible that such associations could be discovered in the near future if certain therapies are shown to work better with autism patients who have a specific genetic variant. Various pharmaceutical treatments are being investigated for ASD, and it is likely that, as with many other drugs, different drugs will work better for some genotypes than others. Another promising area of research is in animal models of autism, where drug treatment regimes genetically tailored to the disease subtype have been able to reverse the disease even in adults, suggesting that “[s]hould these findings generalize to humans, genetically identified pathway therapeutics would become the most important area of future treatment research in ASD.”

Such an approach, both in its discovery and application phases, would require genotyping autism patients. Parents would therefore need to be convinced of the potential benefits of the testing of their child, as well as be assured that there are no significant risks (e.g., confidentiality breaches). In addition, research showing that some genotypes are more treatable than others generally, or with respect to specific therapies, may affect the willingness of insurers to pay for a treatment for a specific patient. This could result in some patients being denied coverage for a therapy they would like to pursue because the insurer has concluded that the therapy is not cost-effective for that particular patient’s genetic profile, although it may be covered for a patient with a different genotype.

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100 One scientist has already reported preliminary findings suggesting promising results in treating children with a particular autism susceptibility gene with the anti-seizure drug valproic acid. Stephan, supra note 78, at 8. The report continued: “These preliminary findings lead one to speculate whether early detection of CNTNAP2 mutation carriers coupled with early intervention could coax children through a critical period in development (12-24 months of age) and allow them to emerge undamaged and continue to develop normally thereafter.”


102 Geschwind, supra note 2, at 375.
E. Neonatal Genetic Screening for Autism

In recent years, there has been a dramatic increase in the number of genetic conditions included in state neonatal screening programs. Many states are now testing all newborn infants for forty or more different genetic conditions. Traditionally, these programs tested only for inborn errors of metabolism that could be successfully treated by dietary or other interventions. The classic example is the recessive genetic condition phenylketonuria (PKU), which if detected early can be managed with a low phenylalanine diet that prevents the severe mental retardation that would otherwise result. Recently, however, there has been “mission creep” in newborn testing programs to include genetic conditions such as cystic fibrosis in which early detection would help delay or minimize symptoms but would not otherwise forestall the disease.

Genetic variants that predispose a child to developing autism may be candidates for neonatal testing, especially if early (pre-symptomatic) treatment of the child can minimize the effects of autism. To date, no autism alleles are included in any state newborn testing program. However, if certain genetic markers are shown to be strong indicators of the subsequent development of autism, there may be strong arguments to incorporate such markers in newborn test programs. As one scientific review recently observed, “[a]s the fraction of ASD for which a specific etiology can be identified increases, one can envision that molecular screening may become part of the newborn screening panel in the not-so-distant future.”

Human and animal studies suggest that early detection of at-risk newborns would be effective for treating or preventing the onset of autism. Moreover, detection of newborns at-risk for subsequent autism development may help parents with planning for future

105 Brkanac et al., supra note 17, at 604.
106 Id.
children. For example, half of all families with a child with Fragile X syndrome have a second child before the condition in the first child has been diagnosed, and in turn, 43 percent of these families had a second child with Fragile X syndrome, 73 percent of which reported that discovering their first child had Fragile X syndrome affected their decision on whether to have another child. Newborn screening might also help to prevent and alleviate the frustration and anxiety that parents experience (sometimes referred to as the “diagnostic odyssey”) when their child experiences developmental delays or other symptoms that have no known cause or diagnosis.

A recent publication described the development of a quick and inexpensive test for the gene mutation causing Fragile X syndrome, which is also the most common single gene associated with autism, that could be used for a population-wide newborn screening program. The authors concluded that

“both in terms of effectiveness and cost ($2 to $5 in reagents and supplies per sample), the current screening test should enable large-scale newborn and/or high-risk screening for expanded alleles of the FMR1 gene. This capability will, in turn, facilitate investigation of the benefits and potential pitfalls of newborn screening and early intervention.”

A pilot study involving neonatal screening for Fragile X of almost 1500 infants born in South Carolina was recently conducted, demonstrating the technical feasibility of such a program.
Significantly, more than 20% of parents in the study refused to have their infants tested, which is a considerably higher refusal rate than other similar newborn screening programs that have requested parental consent.113

One of the issues that will be raised by this possibility is the risk thresholds and degree of validation that should be required to include a particular autism predisposition gene in a neonatal testing program. Not every child carrying an autism predisposing gene will develop autism, so another issue is how the availability of such genetic markers will be integrated with other existing diagnostic criteria to define disease status. There is also the issue of the benefits in terms of treatment outcome in neonatally identifying children predisposed to develop autism. Neonatal screening programs have traditionally been justified by the early detection of metabolic conditions that can be successfully treated if found early enough,114 but the available treatments for ASD are far more limited in their effectiveness at this time. If the principal justification for a future ASD neonatal screening program is primarily to inform parents of the increased risk of their newborn or future children developing ASD, this may represent a significant (and controversial) justification for newborn screening.115 Lastly, there is the issue of whether implementation of such programs should result in reconsideration of the traditional practice, based on the public health imperative of testing for treatable conditions, of not seeking informed consent from parents before testing their newborns.116

As with any genetic test, some level of false positives are to be expected, and the absolute number and relative frequency of false positives versus true positives will likely increase as the number of individuals being tested expands from individual testing of at-risk

113 Lainie Friedman Ross & Kruti Acharya, Policy Considerations in Designing a Fragile X Population Screening Program, 10 GENETICS IN MED. 711, 711 (2008).
115 Bailey, supra note 108, at 9; Bailey, et al., supra note 110, at 3.
116 Ross & Acharya, supra note 114, at 711.
individuals to population-wide newborn screening. There are two types of false positives in an autism genetic testing program. First are true false positives (analytical validity) resulting from laboratory errors where the test result erroneously reports or is misinterpreted to suggest that an individual has an autism susceptibility genotype when in fact they do not (miniscule percent). Second, and more common, is where an individual is correctly identified as having the autism susceptibility genotype, but subsequently does not develop autism (clinical validity). It is this second type of “false positive” that is unique to susceptibility testing for a condition with incomplete penetrance such as autism.

In the case of a false positive diagnosis, it will eventually become clear that the diagnosis was inaccurate, but in the meantime, some significant and lasting negative impacts can occur. Parents will treat the young child differently in response to the (false) test result. What will be the effects on the child’s development and relationship with parents and other family members of the false positive test result?117 The family is likely to experience undue economic stress related to large expenditures for treatment. It is also likely that there will be significant family distress associated with the amount of time and money being spent on treatment and therapy for ASD. Additional stress will likely come from the need to make difficult family decisions, such as whether to have more children, as well as possible discrimination and stigmatization, both by insurance companies and society in general.118 In addition, a child with a susceptibility genotype whose behavioral presentation is considered “odd” may be stigmatized as “autistic” despite not meeting the diagnostic criteria. Conversely, a child with a susceptibility genotype may be excused for “inappropriate” behavior.


118 See Tarja Nyrhinen & Helena Leino-Kilpi, Ethics in the Laboratory Examination of Patients, 26 J. MED. ETHICS 54 (2000).
F. Prenatal Testing/Preimplantation Genetic Diagnosis (PGD) for Autism

It is likely that with the development of biomarkers for autism and the emerging capability for genetic diagnosis, it will soon be possible to test and diagnose fetuses during gestation, and perhaps even embryos prior to implantation, for predisposition to autism. Such options will likely be most appealing to families who have had a previous child diagnosed with autism and seek to avoid having additional children with the condition. In such cases, a family may choose to make some difficult decisions regarding whether to proceed with that fetus or embryo. It is possible that the parents of a fetus, genetically diagnosed with autism, will choose to abort in order to avoid the costs and stresses associated with having an autistic child. However, there are also psychological and physical costs associated with choosing selective abortion, especially later in pregnancy, but these costs are present whether the disease is autism or anything else of concern. Now, if autism were capable of being diagnosed in embryos using PGD, parents could choose to transfer only healthy embryos and to discard those embryos at risk for autism. Using PGO avoids the problem of selective abortion for fetal anomaly (though the problem of abortion qua fetal reduction remains should “too many” embryos implant), but the practice of PGD still raises relevant ethical issues—for instance, balancing the responsibility for the life of the embryo/fetus with the obligation to relieve and prevent suffering as much as possible. The potential for a false positive test result may mean a decision not to proceed with the implantation of the embryo in the case of PGD or the termination of the pregnancy in response to a false positive prenatal test. One ethical issue of this scenario is, therefore, whether the loss of some healthy embryos and fetuses due to false positives is outweighed by the benefits to parents of being able to select against births of children.

119 McMahon et al., supra note 79, at 54; see also Katharine P. Beals, The Ethics of Autism: What’s Wrong with the Dominant Paradigms and How to Fix Them, 9 MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES 32, 32 (2003).

likely to develop autism.

False negatives will also be a problem. Given the complex genetic and environmental etiology of most cases of ASD, prenatal testing will not in the foreseeable future be capable of detecting all fetuses or embryos at risk of developing autism. At-risk parents relying on prenatal genetic testing or pre-implantation genetic diagnosis to prevent the birth of a child with autism may, therefore, have unrealistic expectations and disappointing outcomes from such procedures.121

Another set of issues relates to how the potential for selective abortion of fetuses predisposed to autism will affect the political and moral environment of autism research and clinical application. What impact will it have on adolescents and adults with autism in terms of their and others’ views of their intrinsic value as human beings?122 How will parents view this decision, and how should options be presented to prospective parents, considering that genetic test results are presented as risk estimates (either relative risk or penetrance) and autism is a complex condition?123

The impassioned controversy associated with the possibility of prenatal screening for autism was demonstrated in the United Kingdom, where a flurry of (mostly negative) newspaper stories and commentaries in January 2009 reacted strongly to an indirect comment by Simon Baron-Cohen on the potential feasibility of such testing. Baron-Cohen, director of Cambridge University’s Autism Research Centre, in discussing research findings suggested that there may be a link between fetal testosterone levels and subsequent autism,124 and remarked that he planned to test for this association in larger samples in the future. This was widely (mis)construed as an

121 Lintas & Persico, supra note 18, at 5.

122 See Judy Badner et al., Position Statement on Genetic Discoveries in Autism (undated), available at http://psy-pc120.bsd.uchicago.edu/~jbadner/autagen.htm (statement of families with autism expressing concern about devaluing of people with autism by use of prenatal testing and abortion). But see Beals, supra note 120, at 32 (describing the views of a parent of a child with autism regarding the “taboo” of aborting a fetus at risk for autism).


124 Bonnie Au yeung et al., Fetal Testosterone and Autistic Traits, 100 BRIT. J. PSYCHOL. 1, 1-2 (2009).
endorsement of prenatal testing for autism predisposition.\textsuperscript{125} Criticisms of the potential prenatal screening of fetuses included the infeasibility of an accurate prenatal test given the genetic heterogeneity and variable expression of autistic disorders\textsuperscript{126} and the risk of a new eugenic era that would screen out many talented and extraordinary people with mild ASD.\textsuperscript{127}

\section*{G. Genetics, Autism, and Litigation}

Genetic markers of autism predisposition may also have application in personal injury and other types of litigation. Specifically, a product manufacturer or polluter alleged to be responsible for an environmental or medical exposure that may have caused a plaintiff’s autism could argue that genetics, not exposure, was the primary cause of the condition. Such “alternative causation” claims have already been successfully advanced in a number of cases, including cases involving autism.\textsuperscript{128} For example, in one case, the family of a child with autism alleged that thimerosal in childhood vaccines caused the child’s condition.\textsuperscript{129} Although epidemiology studies failed to support an association between autism and thimerosal in the general population, the child’s family alleged that “some children are genetically susceptible to mercury poisoning and cannot excrete or otherwise eliminate the mercury in the vaccine preservative.” When the child in this case was genetically tested for the putative allele, however, it was found that the child was not genetically susceptible, and hence, the case could not move forward because of lack of proof.

\begin{footnotesize}
\begin{enumerate}
\item\textsuperscript{125} See India Knight, \textit{Soon We’ll be on an Ugly Quest for Perfect Embryos}, SUNDAY TIMES (UK), Jan. 18, 2009, available at \url{http://www.timesonline.co.uk/tol/comment/columnists/india_knight/article5536872.ece}.
\item\textsuperscript{126} Id.
\item\textsuperscript{127} For example, Baron-Cohen stated: “Caution is needed before scientists embrace prenatal testing so that we do not inadvertently repeat the history of eugenics or inadvertently ‘cure’ not just autism but the associated talents that are not in need of treatment.” \textit{Quoted} in Knight, \textit{supra} note 126.
\item\textsuperscript{128} See Gary E. Marchant, \textit{Genetic Data in Toxic Tort Litigation}, 14 J. L. \\ \\ & Policy 7, 8 (2006).
\item\textsuperscript{129} Easter v. Aventis Pasteur, Inc., 358 F. Supp. 2d 574, 575 (E. D. Tex. 2005).
\end{enumerate}
\end{footnotesize}
Other cases have likewise invoked the potential of a genetic cause or contribution to autism to dismiss plaintiffs’ claims that a toxic exposure caused their autism. Often this issue arises when the plaintiffs have ignored genetics and not made any attempt to exclude a genetic cause. For example, in one case the court concluded, in dismissing the plaintiff’s causation claim, “Plaintiffs have made no effort to show that minor plaintiff’s autism did not result from one of the other known causes of autism, such as genetics or prenatal exposure to certain chemicals.”\footnote{Blackmon v. Ame. Home Prods. Corp., 346 F. Supp. 2d 907, 918-19 (S.D. Tex. 2004).}

In another case, the plaintiff’s expert conducted some genetic testing of the plaintiff child with autism to exclude a genetic cause, but the court nevertheless refused to allow the testimony because the expert’s methodology was inconsistent with “the one conclusion that is generally accepted in the medical community with respect to the causation of autism, which is, that its cause is genetic, but that the exact genetic sequence of autism is unknown.”\footnote{Doe 2 v. Ortho-Clinical Diagnostics, Inc., 440 F. Supp. 465, 477 (M.D.N.C. 2006).}

In a non-vaccine case, a Pennsylvania court rejected a plaintiff’s claim that gasoline (and the benzene in that gasoline) caused his autism based in part on expert testimony that the autism was more likely caused by genetics.\footnote{Gasoline from Station Not to Blame for Illnesses, 30(23) PENNSYLVANIA LAW WEEKLY 2 (June 4, 2007).}

Other legal applications of the relationship between genetics and autism are likely. For example, medical malpractice or wrongful birth cases may be brought against healthcare providers who fail to warn or who improperly test prospective parents or their developing fetus for autism predisposition genes. A recent case in New York involved a set of parents with a mother who had a family history of autism and who sued their doctor after giving birth to a child with “autistic traits.”\footnote{Scalisi v. New York Univ. Med. Ctr., 805 N.Y.S.2d 62, 63 (N.Y. App. Div. 2005).}

The parents had used in vitro fertilization with donor eggs to avoid the mother’s potential autism-related genes, but conceived a child with autism nevertheless.\footnote{Id.} The court dismissed the parents’ claim that the doctor, by implanting the fertilized embryo in the mother, had violated the alleged contractual commitment to prevent
autism occurring “uniquely due to plaintiff wife’s genetic tendencies and predisposition to autism.”\textsuperscript{135}

V. CONCLUSION

Rapid and significant progress is being made in the scientific discovery and dissection of the genetic contribution to autism.\textsuperscript{136} At this time, autism genetics remains largely in the research phase, although some autism centers are now starting to integrate genetic testing into their clinical evaluations when certain indications are present.\textsuperscript{137} The argument for widespread genetic testing or screening for ASD given the current status of scientific understanding and diagnostic development is not strong: “In the case of complex disorders, such as ASD, widespread genetic testing would not only be expensive and time-consuming, but also generally inappropriate due to the aetiological complexity” of the condition.\textsuperscript{138}

\textsuperscript{135} Id. at 65.

\textsuperscript{136} Gupta & State, supra note 3, at 435; Abrahams & Geschwind, supra note 56, at 353.

\textsuperscript{137} Herman et al., supra note 49, at 268-69.

\textsuperscript{138} Lintas & Persico, supra note 18, at 1.