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# Imaging Genetics for Our Neurogenetic Future

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**Daniel Z. Buchman & Judy Illes***

## I. INTRODUCTION

In 2009, Tairyan and Illes outlined the potential challenges posed by the growing possibility of combining genetic and neuroimaging information to improve diagnostic and predictive testing of people with disorders affecting the central nervous system.[1] Here, we continue that discussion with a specific focus on the potential power and utility of such combined technologies to accurately predict psychiatric illness, particularly schizophrenia. We review the science of imaging genetics, discuss related ethical issues, such as how endophenotypes construct an at-risk profile, and examine clinical ethics issues surrounding early intervention in the context of the emerging capability. We consider how individuals diagnosed with schizophrenia may embody knowledge from their brains and genomes into an objective-self. We discuss possible implications of imaging genetics for the law and how use of the combined technologies may impact issues of justice. Finally, we argue that while imaging genetics remains a purely laboratory technique today, its potential social uses require



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1. Kate Tairyan & Judy Illes, *Imaging Genetics and the Power of Combined Technologies: A Perspective from Neuroethics*, 164 NEUROSCIENCE 7 (2009).

careful reflection on how the knowledge gained from it may be constructed and interpreted by clinicians, patients, legal scholars, and the lay public.

## II. THE SCIENCE OF IMAGING GENETICS

Brain activation studies combining genetic information and brain signals from human subjects—now known as imaging genetics—were first conducted in early 2000.[2] These studies relied on combined information about the DNA of people and changes in metabolic activity or blood oxygenation as measured during experiments that involved functional imaging of the brain.[3] Susan Bookheimer and colleagues, for example, showed that results on functional Magnetic Resonance Imaging (fMRI) vary depending on the genetic risk of Alzheimer's disease (AD) and may predict the course of cognitive decline.[4] Eric Reiman and colleagues also described the use of fMRI, as well as positron emission tomography (PET), to study brain changes associated with aging in persons with and without the *apolipoprotein E* (APOE) 4 allele, an allele associated with risk of AD.[5] These results, along with others using AD as an early clinical model, suggested that the dual-technology approach could provide early biomarkers for the disease even before the onset of amyloid plaques and neurofibrillary tangles, possibly improve disease tracking, and advance prevention strategies.[6]

The promise of this new, combined capability quickly unleashed a series of studies, such as those on APOE and memory systems, catechol-o-methyltransferase and the

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2. Susan Y. Bookheimer et al., *Patterns of Brain Activation in People at Risk for Alzheimer's Disease*, 343 NEW ENG. J. MED. 450, 450 (2000).

3. *Id.* at 451.

4. *Id.* at 455.

5. Eric M. Reiman, *Linking Brain Imaging and Genomics in the Study of Alzheimer's Disease and Aging*, 1097 ANNALS N.Y. ACAD. SCI. 94, 102–105 (2007); Eric M. Reiman et al., *Declining Brain Activity in Cognitively Normal Apolipoprotein E ε4 Heterozygotes: A Foundation for Using Positron Emission Tomography to Efficiently Test Treatments to Prevent Alzheimer's Disease*, 98 PROC. NAT'L. ACAD. SCI. U.S. 3334, 3335 (2001).

6. *See* John M. Ringman, *What the Study of Persons at Risk for Familial Alzheimer's Disease Can Tell Us About the Earliest Stages of the Disorder: A Review*, 18 J. GERIATRIC PSYCHIATRY & NEUROLOGY 228, 231–32 (2005); Eun Kyoung Ryu & Xiaoyuan Chen, *Development of Alzheimer's Disease Imaging Agents for Clinical Studies*, 13 FRONTIERS BIOSCIENCES 777, 784 (2008); Bart N.M. van Berckel & Philip Scheltens, *Getting a Grip on Alzheimer's Disease: Imaging Amyloid in the Brain*, 6 LANCET NEUROLOGY 204, 205 (2007).

prefrontal cortex, and 5-HTT and the amygdala.[7] Several studies focused on common gene variants known to affect cognitive and behavioral processes within the normal range, and others on conditions such as attention deficit hyperactivity disorder (ADHD),[8] depression,[9] obsessive-compulsive disorder (OCD),[10] anxiety and stress,[11] and schizophrenia.[12] Ahmed Harriri and colleagues used fMRI to study emotional behavior (anxiety, response to fear) in healthy volunteers with different 5-HTT genotypes, as well as a susceptibility gene for affective disorders.[13] They found that participants carrying the less efficient *s* allele of the 5-HTT-promoter gene had an increased amygdala response to fearful stimuli in comparison to subjects homozygous for the *l* allele.[14]

These developments represent a new era in predictive medicine. The actual term "predictive medicine" has been increasingly used by Muin J. Khoury and colleagues to describe new approaches in genomic medicine, where information extracted from an individual's genome identifies whether or not the person is at an increased risk of developing a specific condition, such as mutations of the BRCA1 and BRCA2 genes

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7. *See generally* Venkata S. Mattay & Terry E. Goldberg, *Imaging Genetic Influences in Human Brain Function*, 14 CURRENT OPINION NEUROBIOLOGY 239 (2004) (describing a number of studies using different brain imaging techniques to explore the association between genetic mutations and brain function).

8. *See* Martina T. Mitterschiffthaler et al., *Applications of Functional Magnetic Resonance Imaging in Psychiatry*, 23 J. MAGNETIC RESONANCE IMAGING 851, 851–53 (2006).

9. *Id.* at 853–54.

10. *Id.* at 854–57.

11. Ke Xu et al., *Imaging Genomics Applied to Anxiety, Stress Response, and Resiliency*, 4 NEUROINFORMATICS 51 *passim* (2006).

12. *See* Guiseppe Blasi & Allesandro Bertolino, *Imaging Genomics and Response to Treatment with Antipsychotics in Schizophrenia*, 3 NEUROTHERAPEUTICS 117 (2006); Andreas Meyer-Lindenberg & Daniel R. Weinberger, *Intermediate Phenotypes and Genetic Mechanisms of Psychiatric Disorders*, 7 NATURE REVIEWS NEUROSCIENCE 818 (2006).

13. Ahmed R. Hariri et al., *Imaging Genetics: Perspectives from Studies of Genetically Driven Variation in Serotonin Function and Corticolimbic Affective Processing*, 59 BIOLOGICAL PSYCHIATRY 888, 889 (2006) [hereinafter Hariri et al., *Imaging Genetics*]; Ahmed R. Hariri et al., *A Susceptibility Gene for Affective Disorders and the Response of the Human Amygdala*, 62 ARCHIVES GEN. PSYCHIATRY 146, 146–47 (2005) [hereinafter Hariri et al., *Susceptibility Gene*].

14. Hariri et al., *Imaging Genetics*, *supra* note 13, at 891; Hariri et al., *Susceptibility Gene*, *supra* note 13, at 148.

in breast cancer.[15] Identifying high-risk candidates allows for early intervention and disease management.

The alignment of results from imaging genetics on neurodegenerative disease and psychiatric disorders supports the hypothesis that the combined method has an unprecedented power to predict the development of certain diseases and risky behaviors.[16] Imaging genetics could be used to predict the onset of psychiatric conditions, personality traits, and mental and emotional capacities in a more powerful way than ever before. At this time, however, there still remains much to be studied. Causes of psychiatric conditions are vague at best, and even categorizing disorders remains a significant challenge. Thus, it is realistic and prudent to anticipate increasing study and use of imaging genetics in the years to come,[17] much like other innovations in genetics and neuroscience separately. It is also imperative to anticipate the ethical, social, legal, and clinical problems posed by imaging genetics and to critically examine the value of imaging genetics to accomplish outcomes proposed.

## III. THE ETHICS OF IMAGING GENETICS

Recent advances in knowledge about the neurogenetic contributions to mental illness have provided an impetus for the neuroscience, genetics, and medical communities to contribute to ongoing philosophical, ethical, and legal debates.[18] Ethical issues as they apply separately to genetics and neuroimaging have been a growing focus for applied ethics research, which has contributed to the rise of particular subfields of biomedical ethics focused on the ethics of emerging

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15. *See* Muin J. Khoury et al., *The Continuum of Translation Research in Genomic Medicine: How Can We Accelerate the Appropriate Integration of Human Genome Discoveries into Health Care and Disease Prevention?*, 9 GENETICS MED. 665, 668–69 (2007); Muin J. Khoury et al., *An Epidemiologic Assessment of Genomic Profiling for Measuring Susceptibility to Common Diseases and Targeting Interventions*, 6 GENETICS MED. 38, 43–44 (2004); Muin J. Khoury et al., *Population Screening in the Age of Genomic Medicine*, 348 NEW ENG. J. MED. 50, 50 (2003).

16. Mattay & Goldberg, *supra* note 7, at 239.

17. *See* George J. Annas, *Foreword: Imagining a New Era of Neuroimaging, Neuroethics, and Neurolaw*, 33 AM. J.L. & MED. 163, 163–64 (2007) (discussing the prospective legal uses of neuroimaging).

18. Emily R. Murphy & Judy Illes, *Neuroethics and Psychiatry: New Collaborations for Emerging Challenges*, 37 PSYCHIATRIC ANNALS 798, 803 (2007).

technologies, such as genethics and neuroethics.[19] Here, we examine the ethical issues raised by imaging genetics technologies through the lens of biological psychiatry (biopsychiatry). Biopsychiatry is a subfield within medicine concerned with the function of the central nervous system in mental illness. Since neuroethics is concerned, in part, with ethical issues arising in the application of technologies in the brain sciences, biopsychiatry falls within the scope of neuroethics.[20]

In the past, we and others with interest in neuroethics and biopsychiatry have discussed the ethical dimensions of genetics compared to other approaches to understanding brain health and illness.[21] In one study, Tairyan and Illes performed a comprehensive Medline literature search to explore if ethics has had a presence in journal articles using the specific term "imaging genetics" and found no relevant peer-reviewed publications.[22] To our knowledge, the only publication with content specifically addresses the intersection of ethics and imaging genetics is a book chapter by Turhan Canli.[23] This chapter argues that the future integration of genetic and neuroimaging data would predict narrowly defined forms of behavior better than self-report and other behavioral measures.[24] In response, Tairyan and Illes developed a model building directly on the work of Joshua L. Roffman and colleagues.[25] Following the Roffman et al. continuum from

19. *See id.* at 799.

20. Neil Levy & Steve Clark, *Neuroethics and Psychiatry*, 21 CURRENT OPINION PSYCHIATRY 568, 568 (2008).

21. *See, e.g.*, Thomas Fuchs, *Ethical Issues in Neuroscience*, 19 CURRENT OPINION PSYCHIATRY 600, 601–602 (2006); Judy Illes et al., *ELSI Priorities for Brain Imaging*, 6 AM. J. BIOETHICS, Mar.–Apr. 2006, at W24, W27–28, W29–30; Judy Illes, et al., *From Neuroimaging to Neuroethics*, 6 NATURE NEUROSCIENCE, 205, 205 (2003); Judy Illes, *Neuroethics in a New Era of Neuroimaging*, 14 AM. J. NEURORADIOLOGY, 1739, 1739–40 (2003); Katherine I. Morley et al., *Genetic Screening for Susceptibility to Depression: Can We and Should We?,* 38 AUSTRALIAN & N.Z. J. PSYCHIATRY 73, 77–78 (2004).

22. Tairyan & Illes, *supra* note 1, at 13.

23. Turhan Canli, *When Genes and Brains Unite: Ethical Implications of Genomic Neuroimaging*, *in* NEUROETHICS: DEFINING THE ISSUES IN THEORY, PRACTICE, AND POLICY 169–83 (Judy Illes ed., 2006).

24. *Id.* at 181.

25. Tairyan & Illes, *supra* note 1, at 2–5. For further information on what Tairyan and Illes's model is based on, see Joshua L. Roffman et al., *Neuroimaging-Genetic Paradigms: A New Approach to Investigate the Pathophysiology and Treatment of Cognitive Deficits in Schizophrenia*, 14

genes to clinical features with neuroimaging at the interface, Tairyan and Illes modified the original framework to include some potential ethical issues.[26] These include the proposed challenges of disease differentiation, incidental findings, values of privacy and autonomy, societal beliefs and attitudes, resource allocation for research and health care, and commercialization.[27] Similarly to the result of the Roffman et al. continuum that produces clinical practice considerations, Tairyan and Illes point to preliminary considerations for health care, social justice, and policy.[28]

Deeper reflection on the ethics of imaging genetics in biopsychiatry is a logical next step. An ethically responsible approach to address the possible social, clinical, and legal implications of current scientific research will require an assessment of the proposed promises and potential outcomes of that research. A close examination of how knowledge produced by imaging genetics may have an impact on the identity of the individual will facilitate thinking of how the law, society, and psychiatry define the normal brain and mental illness, and label someone as "at risk." For example, a statistical deviation from the norm in psychiatric imaging research does not necessarily confirm pathology[29] (for example, depression), or rather, somewhat rhetorically, does not confirm that one has a "depressed" brain as opposed to a "normal" brain.[30] There is a tendency toward this binary distinction even though a so-called "normal" brain has yet to be described empirically. Imaging genetics may consequently lead to a paradigmatic shift in psychiatric classification by constructing "normal" and "abnormal" from a complex integration of correlations statistics and risk ratios.

How might advances in imaging genetics provide empirical information advancing the understanding of human subjectivity and the self, as well as the application of emerging predictive technologies in biological psychiatry? Psychiatric illness may highlight the basis of human subjectivity, such as

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HARV. REV. PSYCHIATRY 78 (2006).

26. Tairyan & Illes, *supra* note 1, at 3.

27. *Id.* at 4.

28. *Id.*

29. Alison C. Boyce, *Neuroimaging in Psychiatry: Evaluating the Ethical Consequences for Patient Care*, 23 BIOETHICS 349, 350 (2009).

30. *See* Joseph Dumit, *Is It Me or My Brain? Depression and Neuroscientific Facts*, 24 J. MED. HUMAN. 35, 37 (2003).

the neurological and genetic underpinnings of selfhood. We will specifically examine these questions using the current diagnostic construct of schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[31] as a model.

### A. THE SCHIZOPHRENIA SPECTRUM AND IMAGING GENETICS

Schizophrenia affects up to 1 percent of the population, is up to 81 percent heritable, and is characterized by hallucinations, delusions, and cognitive deficits.[32] Many individuals who experience symptoms of schizophrenia have a difficult time negotiating their sense of integrated and active intentionality.[33] More specifically, thoughts, actions, and the self may be perceived as under the control of an external force or being.[34] Conversely, the self may be perceived as transcendent, omnipotent, or even prophetic.[35] Schizophrenia is a useful case example because of the extensive research into genetics and neuroscience separately and jointly, the major health impact on the population, the putative role of biological factors in its etiology, and the complex interaction of both genetics and environment in the causation and pathogenesis of disease.

We restrict our discussion of schizophrenia to the prodromal phase that occurs prior to the onset of symptoms, when the individual first notices some change in him or her self, and the first episode or break. The first episode tends to occur in men in their late teens or early twenties and in women a few years later.[36] Depending on the legal age of adulthood in a person's jurisdiction, individuals may still be a minor when symptoms appear. For our purposes, the prodromal phase represents the core features of schizophrenia, as opposed to the

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31. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 298 (4th ed. Text Revision 2000) [hereinafter DSM-IV-TR].

32. Patrick F. Sullivan et al., *Schizophrenia as a Complex Trait: Evidence from a Meta-Analysis of Twin Studies*, 60 ARCHIVES GEN. PSYCHIATRY 1187, 1190 (2003).

33. Thomas Fuchs, *The Temporal Structure of Intentionality and Its Disturbance in Schizophrenia*, 40 PSYCHOPATHOLOGY 229, 234 (2007).

34. *Id.* at 233–34.

35. *See* Louis A. Sass, *Schizophrenia, Self-Consciousness and the Modern Mind*, *in* MODELS OF THE SELF 319, 320 (Shaun Gallagher & Jonathan Shear eds., 1999).

36. DSM-IV-TR, *supra* note 31, at 307.

symptoms that individuals suffer in a more chronic stage of disease that may be confounded by years of social isolation and the long-term effects of older generation anti-psychotics.[37] Given the possible predictive power of imaging genetics, and the possible benefit to the individual of early detection and intervention, it is here that we focus our attention.

### B. ENDOPHENOTYPES AND THE CONSTRUCTION OF RISK

Identifying individuals at risk for a particular medical or social condition such as depression or poverty is common practice in many fields and not unique to psychiatry. In the clinical neurosciences, recent focus has been placed on biomarkers and endophenotypes. A biomarker is a biological marker that is "objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."[38] Endophenotypes are "intermediate phenotypes . . . measurable (though often subclinical), heritable biological markers that relate both to underlying pathophysiology and to clinical symptoms."[39] In the past, both psychiatric research and clinical practice have encountered difficulties with identifying a biological vulnerability to this mental illness. The creation of endophenotypes may ease this complexity by identifying biological markers indicating a susceptibility to developing a mental illness prior to the onset of symptoms.[40] The use of neuroimaging in the endophenotype analysis of complex psychiatric diseases may shed light on the biological mechanisms underlying these conditions.[41] As expected, endophenotypes are becoming an increasingly critical notion in biological psychiatry.

Schizophrenia and other psychotic disorders are currently

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37. *See* DAN ZAHAVI, SUBJECTIVITY AND SELFHOOD 134 (2005) ("[E]arly symptoms detectable in the first (initial) prodromal stage . . . might, in a much sharper manner, express the essential core of the illness."); Josef Parnas & Louis A. Sass, *Self, Solipsism, and Schizophrenic Delusions*, 8 PHIL. PSYCHIATRY & PSYCHOL. 101, 117, 117n.1 (2001) (describing the prodromal phase as "heralding the onset of imminent psychosis" and suggesting that etiological research focus on the early stages of the disease).

38. Biomarkers Definitions Working Group, *Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 89, 91 (2001).

39. Roffman, *supra* note 25, at 79.

40. *Id.*

41. *Id.*

defined and diagnosed based on symptoms as classified by the DSM-IV and the International Classification of Disease (ICD-10)[42], in addition to the reports of patients and their families. Accordingly, identifying a biomarker or endophenotype through neuroimaging genetic tools, rather than relying on symptoms checklists and clinical phenomenology, may provide a more precise method of prediction and diagnosis.

Recent studies of imaging genetics in schizophrenia have focused on the biomarkers of COMT, [43] PCM1, [44] and DISC1.[45] Michael F. Egan and colleagues have, examined the relationship between functional polymorphisms of the catechol-O-methyltransferase (COMT) gene and regulation of prefrontal dopamine that is associated with the genetic risk of schizophrenia.[46] The authors studied the effect of COMT genotype on prefrontal physiology during a working memory task and found that a low met allele load (number of mutations) consistently predicted a more efficient physiological response in the prefrontal cortex.[47]

Several imaging studies with adolescents believed to be at high risk for schizophrenia found notable structural and functional impairments observed in key brain regions.[48]

42. WORLD HEALTH ORGANIZATION, INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEM (10th revision 2007), *available at* http://apps.who.int/classifications/apps/icd/icd10online/.

43. Michael F. Egan et al., *Effect of COMT Val$^{108/158}$ Met Genotype on Frontal Lobe Function and Risk for Schizophrenia*, 98 PROC. NAT'L ACAD. SCI. U.S. 6917, 6920 (2001).

44. Hugh M. D. Gurling et al., *Genetic Association and Brain Morphology Studies and the Chromosome 8p22 Pericentriolar Material1 (PCM1) Gene in Susceptibility to Schizophrenia*, 63 ARCHIVES GEN. PSYCHIATRY 844, 849 (2006).

45. Neeltje E. van Haren et al., *Genetic Genes and Structural Brain Imaging in Schizophrenia*, 21 CURRENT OPINION PSYCHIATRY 161, 163 (2008).

46. Egan et al., *supra* note 43, at 6917.

47. *Id.* at 6919.

48. *See, e.g.*, Stefan J. Borgwardt et al., *Structural Brain Abnormalities in Individuals with an At-Risk Mental State Who Later Develop Psychosis*, 51 BRIT. J. PSYCHIATRY s69, s72–73 (2007); Sven Haller et al., *Can Cortical Thickness Asymmetry Analysis Contribute to Detection of At-Risk Mental State and First-Episode Psychosis?: A Pilot Study*, 250 RADIOLOGY 212, 217 (2009); Peter Milev et al., *Initial Magnetic Resonance Imaging Volumetric Brain Measurements and Outcomes in Schizophrenia: A Prospective Longitudinal Study with 5-Year Follow-Up*, 54 BIOLOGICAL PSYCHIATRY 608, 612 (2003); Christos Pantelis et al., *Neuroanatomical Abnormalities Before and After Onset of Psychosis: A Cross-Sectional and Longitudinal MRI Comparison*, 361 LANCET 281, 285–86 (2003).

Specifically, participants had low levels of grey matter volume in the frontal and temporal lobes and cingulate gyrus,[49] key areas associated with cognition and executive function such as decision-making and self-monitoring. Most importantly, these studies demonstrated that researchers can construct an image of risk from a brain scan that could be predictive of psychosis or schizophrenia.[50]

The implications of both neuro- and gene-profiling of individuals very early in life for a psychiatric illness might qualitatively differ from the implications of profiling other medical conditions in childhood and adolescence.[51] An extensive literature discusses the ethics of clinical and non-clinical uses of pediatric neuroimaging, from the fetus to the neonate to the adolescent.[52] Although a number of ethical issues continue to be discussed, this paper is concerned with the ethical duties to minimize risk and maximize benefit, as well as the duty to appropriately and thoroughly describe the risks and benefits of imaging genetics for potential translation from bench to bedside.[53] While some risks are associated with safety and efficacy, other ethical challenges involve describing the information produced by imaging genetics completely, accurately and meaningfully.[54]

If endophenotypes for schizophrenia are detected during pediatric screening, children might be subjected to invasive and potentially harmful interventions. For example, prescribing psychopharmaceutical medication for children with conditions such as attention deficit/hyperactivity disorder is on the rise.[55] Early intervention in psychosis has a demonstrable benefit for

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49. *See, e.g.*, Pantelis et al., *supra* note 48, at 285.

50. *See, e.g.*, *id.* at 287 (stating that data from the authors' study raise the possibility that MRI or other methods can determine which individuals at high risk for schizophrenia will develop psychosis).

51. Ilina Singh & Nikolas Rose, *Biomarkers in Psychiatry*, 460 NATURE 202 (2009).

52. *E.g.*, Andrew Fenton et al., *Ethical Challenges and Interpretive Difficulties with Non-Clinical Applications of Pediatric fMRI*, 9 AM. J. BIOETHICS 3, 6–8 (2009).

53. *See* Jocelyn Downie & Jennifer Marshall, *Pediatric Neuroimaging Ethics*, 16 CAMBRIDGE Q. HEALTHCARE ETHICS 147, 149 (2007).

54. *Id.*

55. *See* Rick Mayes et al., *ADHD and the Rise in Stimulant Use Among Children*, 16 HARV. REV. PSYCHIATRY 151, 151 (2008) (noting the "unprecedented jump" that occurred in the 1990s in the number of children using drugs such as stimulants for ADHD).

prognosis.[56] Therefore, it is foreseeable that children who are carriers of certain biomarkers or endophenotypes for schizophrenia may be prescribed psychotropic medications prior to the onset of symptoms. This clinical evaluation requires a particularly careful examination because of the recent Food and Drug Administration warnings of the increased risk of suicide in children and adolescents who are prescribed selective serotonin/norepinephrine reuptake inhibitors (e.g., fluexotine and venlafaxine).[57] In addition, children metabolize psychopharmaceuticals differently than adults, likely due to ways in which genetics modulate the activity of enzymes in drug metabolism.[58] The administration of pharmaceuticals on the basis of predictive diagnostic criteria could result in the emergence of an iatrogenic disorder.[59] Over-treating with antipsychotics based on a vague understanding of risk variables is unsupported.

Individuals tend to experience their first episode of psychosis at an age when the law may not permit them to provide consent to their own treatment.[60] Thus, early identification of biomarkers may raise questions about the decisional capacity of both children and adolescents, as well as their ability to appreciate the risks and benefits associated with early intervention for psychosis. Concerns about mental competence may be particularly troublesome for some older adolescents who may be beginning to enjoy some liberty in other areas of their lives and, perhaps, even some autonomy in their own medical decision-making. Balancing duties to protect children and adolescents when they may be most vulnerable, while negotiating space for autonomy, will be a significant challenge.

Skepticism exists about whether data averaged over groups of participants, a common practice in research studies

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56. Richard Jed Wyatt & Ioline D. Henter, *The Effects of Early and Sustained Intervention on the Long-Term Morbidity of Schizophrenia*, 32 J. PSYCHIATRIC RES. 169, 170 (1998).

57. Mark Olfson et al., *Antidepressant Drug Therapy and Suicide in Severely Depressed Children and Adults: A Case-Control Study*, 63 ARCHIVES GEN. PSYCHIATRY 865, 865, 867 (2006).

58. Anders Rane, *Phenotyping of Drug Metabolism in Infants and Children: Potentials and Problems*, 104 PEDIATRICS 640 *passim* (1999).

59. Walter Glannon, *Neuroethics*, 20 BIOETHICS 37, 44 (2006).

60. *See* DSM-IV-TR, *supra* note 31, at 307 (stating that the age of onset for schizophrenia typically begins in the late teens).

with either adults or children, can truly predict pathology in a robust way for a specific person.[61] Research that examines endophenotypes in schizophrenia tends to have limited effect sizes, as studies rely on group averages with respect to brain features[62] and use small samples. Therefore, the picture produced by imaging studies of the "schizophrenic" brain, for example, is not of the brain of any specific person, let alone the brain of an actual human being.[63] Research that seeks to elucidate pathology on an individual level must consider the differences of human structural, metabolic and chemical brain signatures; clinically this diversity will have an inevitable impact on monitoring of therapeutic interventions.[64] If used in isolation, endophenotypes may not be strong indicators of the existence of pathology: the endophenotype represents a correlation, rather than a causal explanation.[65] Due to the high rates of intra- and inter-individual variability, at this time it would be premature to depend on images of brains with activity linked to genetic effects as objective clinical or legal evidence.[66]

The identification of clinically relevant endophenotypes will require a combined focus on clinical phenomenology, narratives, personal and family history, molecular and genetic markers, neuroanatomical, neurophysiological, and neurocognitive processing mechanisms.[67] Biomarkers, and by extension endophenotypes, will thus remain merely a statistical probability for the time being.

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61. *See* Grace E. Jackson, *A Curious Consensus: "Brain Scans Prove Disease"?*, 8 ETHICAL HUM. PSYCHOL. & PSYCHIATRY 55, 57–58 (2006).

62. *See id.* at 58.

63. *Id.*

64. Laura Huber, *Imaging the Brain: Visualising "Pathological Entities"?: Searching for Reliable Protocols Within Psychiatry and Their Impact on the Understanding of Psychiatric Diseases*, 6 POIESIS & PRAXIS 27, 32 (2009).

65. *See id*. at 33–34.

66. *See* Dara S. Manoach et al., *Test-Retest Reliability of a Functional MRI Working Memory Paradigm in Normal and Schizophrenic Subjects*, 158 AM. J. PSYCHIATRY 955, 958 (2001) (stating that study findings suggest it is important to demonstrate reliability in repeated fMRI studies of schizophrenic subjects).

67. *See* Jason Scott Robert, *Gene Maps, Brain Scans, and Psychiatric Nosology*, 16 CAMBRIDGE. Q. HEALTHCARE ETHICS 209, 215–16 (2007) (advocating an integrative approach to the identification of endophenotypes).

### C. IMAGING GENETICS AND THE OBJECTIVE-SELF IN SCHIZOPHRENIA

Both health professionals and the lay public have a vested interest in achieving positive health outcomes. Since scientific and technological research is the portal to modern knowledge about health and illness, the desire for improved health outcomes may result in an increased attribution of objectivity by physicians and patients to brain scans and genetic data.[68] This dialectical process is what Joseph Dumit refers to as the objective-self: the "set of acts that concerns our brains and our bodies deriving from received-facts of science and medicine."[69] The objective-self is how people understand brains and bodies as biologic material. Objective-selves challenge generally accepted notions of normality as the "normal" brain is compared to its abnormal counterpart.[70]

The possible consequences of imaging genetics screening in psychiatry, and for schizophrenia specifically, requires ethical examination of the potential impact of an objective-self. One concern is the communication of risk. Inappropriate communication of imaging genetics information may affect a person's perception of his ability to manage symptoms. Statistics, including measures of probability and risk, are difficult to comprehend, and framing effects—especially as people try to comprehend odds ratios—can influence their interpretation of the information.[71] Using imaging genetics tools to screen for psychopathology may inadvertently elevate levels of fear and anxiety about developing a mental illness. The fear of being at risk for a self-altering disorder such as schizophrenia may affect choices a person makes for education, employment, or other social and life plans. Indeed, a disorder of the self may also impact the extent to which ambitious life goals are supported by friends and family.[72]

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68. Christian G. Huber, *Interdependence of Theoretical Concepts and Neuroimaging Data*, 6 POIESIS & PRAXIS 203, 205 (2009).

69. Dumit, *supra* note 30, at 39.

70. *See id.* at 39–40.

71. *See* A. J. Lloyd, *The Extent of Patients' Understanding of the Risk of Treatment*, 10 QUALITY HEALTH CARE i14, i17 (2001) (stating that "[w]hile clinicians typically report risk information as percentages or relative risks, . . . people may code information qualitatively.").

72. Cheryl Corcoran et al., *Prodromal Interventions for Schizophrenia Vulnerability: The Risks of Being "At Risk"*, 73 SCHIZOPHRENIA RES. 173, 177 (2005).

Moreover, the way in which the candidate gene is expressed in the brain may become intimately linked with personal identity. The objective-self and identity may be considered schizophrenic if both the genes and the brain are affected. A schizophrenic identity may be further embedded in societal and cultural attitudes, and in the experiences of an affected individual in the world.

### D. IMAGING GENETICS AND FALSE POSITIVES

Imaging genetics is a combined process: it involves both a genome scan and a brain scan, and the two types of knowledge produced are expected to be in a causal relationship. Given the increasing trend toward genome-wide association studies in biopsychiatry, there is a rapidly growing pool of information on the neuronal expression of genes. The identification of numerous prospective endophenotypes raises the problem of false positives, because candidate genes—including those not well understood—will be directly linked to imaged brain structures and function. For our purposes, false positives will be defined in two ways. First, false positives will be erroneous conclusions made after a gene variant of unclear relevance is linked with high-dimensional imaging information.[73] This extends to a second, looser definition, borrowing from Jerome Wakefield, that false positives may be "non-disorder" conditions that meet some or the majority of the criteria for a disorder such as schizophrenia.[74] The individual is thus treated—in both the medical and relational sense—as a member of the diagnostic group.

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73. Andreas Meyer-Lindenberg et al., *False Positives in Imaging Genetics*, 40 NEUROIMAGE 655, 659 (2008) (stating that "given the absence of reliable information on the heritability and reliability of the majority of imaging phenotypes in current usage, a statistically significant result in neuroimaging is by itself not sufficient to establish that a given polymorphism is functional, and the complex nature of psychiatric disease predicts that the isolated genetics evidence for association will usually not be unequivocal for a given variant.").

74. Jerome C. Wakefield & Michael First, Clarifying the Distinction Between Disorder and Non-Disorder: Confronting the Overdiagnosis ("False Positives") Problem in DSM-V, *in* ADVANCING DSM: DILEMMAS IN PSYCHIATRIC DIAGNOSIS 23, 24 (Katharine A. Phillips et al. eds., 2003); *see generally*, ALAN V. HOROWITZ & JEROME C WAKEFIELD, THE LOSS OF SADNESS: HOW PSYCHIATRY TRANSFORMED NORMAL DISORDER INTO DEPRESSIVE DISORDER (2007); Jerome C. Wakefield, *What Makes a Mental Disorder Mental?*, 13 PHIL. PSYCHIATRY & PSYCHOL. 123, 129 (2006) (arguing that "some mental disorders may not involve neurologic dysfunction").

At this time, only a few select biomarkers and endophenotypes represent a somewhat reliable indication of increased risk for psychiatric illness. Even if the reliability, validity, and specificity of imaging genetic tests are improved for schizophrenia, some number of false positives and diagnostic errors will still occur. Effective treatments must be developed in order for false positive rates even as low as 5 percent[75] to be tolerated.[76] How the information produced by imaging genetics, including false-positive results, will be handled by the law is the topic to which we turn next.

## IV. IMPLICATIONS FOR THE LAW AND JUSTICE

### A. NEUROGENETICS AND THE LAW

There has been considerable discussion in academic literature about the current and potential uses of neuroscience and neurotechnology in the legal system,[77] particularly because of the concern that the law has with mental states.[78] When DNA evidence was first admitted in the courts, it became a powerful evidentiary tool, not because it demonstrated the existence of mental states, but because it represented seemingly objective and indisputable hard facts.[79] The

75. *See* Meyer-Lindenberg et al., *supra* note 73, at 659 (stating that expected statistical rate of false positives is 5 percent).

76. *Cf.* Judy Illes et al., *Prospects for Prediction: Ethics Analysis of Neuroimaging in Alzheimer's Disease*, 1097 ANNALS N.Y. ACAD. SCI. 278, 283 (2007) (stating that, in the context of neuroimaging for Alzheimer's Disease, "[t]he ethical issues pertaining to which clinical populations should be tested will depend largely on whether or not a definitive treatment becomes available.").

77. *See, e.g.*, Neil K. Aggarwal, *Neuroimaging, Culture and Forensic Psychiatry*, 37 J. AM. ACAD. PSYCHIATRY& L. 239, 240 (2009); Henry T. Greely & Judy Illes, *Neuroscience-Based Lie Detection: The Urgent Need for Regulation*, 33 AM. J.L. & MED. 377, 390–94, 405–20 (2007) ); Joshua Greene & Jonathan Cohen, *For the Law, Neuroscience Changes Nothing and Everything*, 359 PHIL. TRANSACTIONS ROYAL SOC'Y: BIOLOGICAL SCI. 1775, 1775–76, 1778–81 (2004); Owen D. Jones, *Law, Evolution, and the Brain: Applications and Open Questions*, 359 PHIL. TRANSACTIONS ROYAL SOC'Y: BIOLOGICAL SCI. 1697 *passim* (2004); Susan M. Wolf, *Neurolaw: The Big Question*, 8 AM. J. BIOETHICS 21, 21–22 (2008).

78. *See* Greene & Cohen, *supra* note 77, at 1775.

79. *See* Jay D. Aronson, *DNA Fingerprinting on Trial: The Dramatic History of a New Forensic Technique*, 29 ENDEAVOUR 126, 128 (2005) (stating that "by early 1986, DNA evidence had been accepted by the [U.K.] magistrate's court as valid and reliable").

combined use of DNA and imaging genetics information might provide a similarly powerful tool, and, instead, may offer more reliable and valid evidence of the existence of limited mental capacity or cognitive deficits commonly associated with a condition, even before an individual is symptomatic. Initially, the threat of introducing DNA evidence was an influential and intimidating tactic, which, at times, distracted the jury's attention from its status as an "untried and untested technology."[80] At the present time, use of imaging genetics information as legal evidence is far from reality, particularly since neuroimaging data themselves are not ready for legal prime time.

The presence or absence of genetic or clinical traits associated with a condition such as schizophrenia does not itself cause illicit behavior or even a disorder itself.[81] Many individuals who are not carriers or do not have full-blown psychiatric conditions have committed many crimes. Conversely, those with the genes or condition may commit no illicit acts. What the presence of risk traits does imply, however, is that the pre-symptomatic individual may already possess certain difficulties relating to cognitive function and mental capacity. A positive result in an imaging genetics study could be used to argue against the mental competence to stand trial.[82] In other cases, this information may be used to argue that the individual does not have the requisite *mens rea* to be found guilty of certain offense, and thus can be used to support a less retributive sentence.[83]

### B. NEUROGENETICS AND JUSTICE

A more immediate and pragmatic challenge posed by the production of imaging genetics knowledge concerns the ethical issue of justice. Justice necessitates consideration of the potential harms that may arise for individuals or communities resulting from research participation, or in clinical

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80. *Id.* at 126; Patrick Haines, *Embracing the DNA Fingerprint Act*, 5 J. ON TELECOMM. & HIGH TECH. L. 629, 640 (2007).

81. Jerome C. Wakefield, *The Measurement of Mental Disorder*, *in* A HANDBOOK FOR THE STUDY OF MENTAL HEALTH 29, 39–40, 57 (Alan V. Horwitz & Teresa L. Scheid eds., 1999).

82. Walter Sinnot-Armstrong et al., *Brain Images as Legal Evidence*, 5 EPISTEME 359, 360 (2008).

83. Greene & Cohen, *supra* note 77, at 1775, 1783; Sinnot-Armstrong et al., *supra* note 82 at, 360.

implementation of, or interaction with, the technology. In the spirit of John Rawls's "distributive justice,"[84] justice involves fairness in not only the equitable distribution of risks, but also in the equitable distribution and access to research benefits and clinical technology.

The ethics of predictive genetics in the United States has been widely discussed, especially in the context of insurability and employability.[85] Similar scholarly and policy initiatives have been emerging for neuroimaging. Key ethical issues are privacy and confidentiality.[86] One issue of continuing concern is how health insurers and employers may use genetic or imaging knowledge that suggests a possibility of a pre-existing disorder to prevent people from accessing health insurance. Diagnosing asymptomatic individuals early in life may raise concerns similar to those at issue raised by newborn screening. Protection of confidentiality and ensuring privacy of genetic and imaging information are of particular importance. For a highly stigmatized condition such as schizophrenia, these challenges are compounded.

Positive steps have recently been taken at the federal level with the enactment of the Genetic Information Nondiscrimination Act (GINA).[87] Though not a panacea, GINA moves to ensure that results from predictive genetic testing will not be an impediment to receiving medical insurance or gaining employment.[88] While ethical issues of discrimination, privacy, and confidentiality of information are not unique to schizophrenia or genetics, as technologies such as imaging genetics become more sensitive and powerful, information derived from the genome will impact all aspects of health care

84. *See generally* JOHN RAWLS, JUSTICE AS FAIRNESS: A RESTATEMENT (Erin Kelly ed., 2001).

85. *E.g.*, Paul W. Brandt-Rauf & Sherry I. Brandt-Rauf, *Genetic Testing in the Workplace: Ethical, Legal, and Social Implications*, 15 AM. REV. PUB. HEALTH 139 (2004); K.G. Fulda & K.Lykens, *Ethical Issues in Predictive Genetic Testing: A Public Health Perspective*, 32 J. MED. ETHICS 143, 144 (2006).

86. *See, e.g.*, Jinger G. Hoop, *Ethical Considerations in Psychiatric Genetics*, 16 HARV. REV. PSYCHIATRY 322, 329 (2008) (discussing the potential unfairness that genetic information could produce in the insurance context).

87. Pub. L. No. 110–233, 122 Stat. 188 (codified as amended in scattered sections of 29 U.S.C.); *see also* Kathy L. Hudson et al., *Keeping Pace with the Times – The Genetic Information Nondiscrimination Act of 2008*, 358 NEW ENG. J. MED. 2661, 2661 (2009).

88. Hudson et al., *supra* note 87, at 2662.

and social services.

If imaging genetics proves both reliable and valid, existing divisions in access to health care will also be affected. If imaging genetic tests were to become a standard of care or commercialized, or made available to individuals universally or through third-party coverage, the potential impact on the public health systems could be vast. By contrast, because psychiatric illness disproportionately affects lower-income populations[89] and public forms of health care insurance remain hotly debated, financial barriers might significantly limit access to neuroimaging genetic technologies for the very people most likely to benefit from them.

Large-scale screening procedures can only be justified on social, economic, and ethical grounds if sustainable follow-up is in place for people identified as being high-risk and if a reliable, effective, and safe treatment is available.[90] Scientific and technological development of imaging genetics, with robust clinical trials testing early intervention for asymptomatic high-risk individuals, will determine whether early intervention for those identified by imaging genetics will reduce morbidity and mortality, and will improve quality of life.[91]

## V. CONCLUSION

Humans have an insatiable appetite for information and innovation. History shows that when a new medical device or method is rolled out after proven validity in the laboratory, demand for that innovation is great. Currently, the ability of neuroscience and genetics—applied together or separately—to offer a robust explanation of psychiatric disorders is not yet demonstrated due to many remaining methodological and epistemological limitations.[92] As Meyer-Lindenberg et al. assert:

> [G]iven the absence of reliable information on the heritability and

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89. *See* NAT'L CTR FOR HEALTH STATISTICS, U.S. DEP'T OF HEALTH & HUMAN SERVS., HEALTH, UNITED STATES, 2008 WITH SPECIAL FEATURE ON THE HEALTH OF YOUNG ADULTS 30 (2008).

90. *See* Illes et al., *supra* note 76 at 283–85 (proposing criteria for use of screening for Alzheimer's disease).

91. *See* Wayne D. Hall et al., *The Prediction of Disease Risk in Genomic Medicine*, 5 EUR. MOLECULAR BIOLOGY ORG. REP. (SPECIAL ISSUE) S22, S25 (2004).

92. *See generally* Wakefield & First, *supra* note 74, at 23–56 (noting the shortcomings of the DSM definition of mental disorder).

> reliability of the majority of imaging phenotypes in current usage, a statistically significant result in neuroimaging is by itself not sufficient to establish that a given polymorphism is functional, and the complex nature of psychiatric disease predicts that the isolated genetics evidence for association will usually not be unequivocal for a given variant.[93]

The ability to better predict psychiatric illness could lead to improved diagnosis and treatment through the early identification of individuals who are at high biological risk. Benefits may follow from earlier treatment options, both for individuals and for society more generally. At the very least, imaging genetics may reinforce the strong organic component of psychiatric illness. However, risks of a biopsychiatry that focuses only on the combination of abnormal brain mechanisms and genetics, rather than on the integrated person as a being-among-others, must be minimized. It is currently too early to suggest that imaging genetics will become a clinical reality or tool for legal decision-making; too many scientific and technological problems regarding the application of the technology remain to be solved. Nonetheless, now is the time to consider the ethical, legal, and social issues, in order to ensure benefit and impact for the future. There has been too little consideration of these issues in imaging genetics—a powerful technology linking neuroscience and genetics. This gap can be filled by interdisciplinary collaboration and attention to public health and legal challenges. Efforts to fill that gap must integrate societal, clinical, and legal implications in a way that is both pragmatic and open-minded.[94] Meanwhile, the science calls for more work. Further evaluation and empirical testing is needed for many conditions that affect executive function and decision-making, including schizophrenia.

93. Meyer-Lindenberg et al., *supra* note 73 at 659.

94. Adrian Carter et al., *Scare-Mongering and the Anticipatory Ethics of Experimental Technologies*, 9 AM. J. BIOETHICS 47, 48 (2009) (arguing for a focus on plausible potential harms from participation in clinical trials).