An Investigation of the Ethical Issues Presented by the Use of Neuroscience and Genomics in the Diagnosis and Treatment of Psychosis: The Need for Integrated Bioethics

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Contents

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Abstract

In recent years, technological innovation has rekindled the interest in the neurobiology of psychosis. The convergence of neuroscience, next-generation genomics, and data science holds promise to revolutionise how we understand and treat psychotic illness. Yet, moral challenges arise from this endeavour. This thesis presents an ethico-legal investigation into how technology is reshaping neurobiological approaches to psychosis. I first survey the literature on the ethical, legal, and social issues that characterise neuroscientific and genomic approaches to psychosis. In Article one, I argue that we ought to respond to technological convergence by developing an integrated approach focused on the assessment of individual vulnerabilities. I then discuss empirical findings from my fieldwork: in Article two, I show that researchers and health professionals contend that substantial moral challenges arise from having access to neurobiological information because this affects individuals' identity; in Article three, I show that mental health carers demand novel and effective interventions, yet they argue that technological innovation could benefit or harm those who suffer from psychosis depending on whether their needs are appropriately assessed and met. In Article four, I investigate how we should regulate the use of machine learning for psychosis prediction with reference to the jurisdiction of England and Wales; I argue that this is dependent upon the interpretation of the notions of 'risk' and 'harm' in research regulation and mental health law. I conclude by discussing some methodological challenges of empirical ethics in psychiatry, by reflecting on the theoretical implications of the concepts of vulnerability, identity, and care for ethical theory, and by examining the significance of the rise of artificial intelligence for bioethics. Overall, I argue that we ought to work towards a more nuanced understanding of the ethics of technological innovation in psychiatry. We need improved collaboration between ethico-legal scholars and social actors, as well as the revised notions and moral principles that can emerge from this collaboration, in order to ensure that our increased understanding of the neurobiology of psychosis might truly benefit, and not harm, those who suffer from mental illness.

Declaration

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True love will find you in the end

Daniel Johnston

1. INTRODUCTION

1.1 General foreword

The reason why I chose to focus my research on psychosis and schizophrenia is twofold. As for other choices in my professional life, it involves at the same time personal and professional factors. By describing the occurrences that brought the ethical issues arising from the management of psychotic disorders to my attention, I hope that the reader will get a sense of the relevance of this topic for bioethical inquiry and of its significance for my doctoral research.

I grew up in Italy, in a town situated on the banks of a river and surrounded by a national park. The park is beautiful. Tall trees gradually descend towards the river. They provide shade and refreshment in the hot summer days. The river's blue waters are generous to anglers. People in my hometown have always inhabited the banks of the river. Small cabins populate the park and the river's banks. People visit the park after work, on the weekends, during holidays. They go for walks, relax, and share some time. We learned to do that from our grandparents. As a student in my early twenties, I used to visit the park to take long walks. Lazy summer afternoons far away from the real world. One day, while I was wandering through the park, I learned of a person who had recently seemed changed, distant, and withdrawn. That person had started hearing voices. I was left utterly puzzled. I had no idea of what that meant. Literally no idea. I did not know that someone could hear voices. I could think of very few rational explanations for that. I decided to try to understand what 'hearing voices' could mean. I found out about psychosis, psychotic disorders, and schizophrenia. I had heard those words in movies and on television, but I did not know what they meant for real. Although being a young university student, I did not know what those words meant. To me, this person had simply gone 'mad'. Which is a label I later learned people use to name something they do not know, nor understand.

Years later, after having completed a Master's in Bioethics, I was hired as a research assistant at the Department of Psychiatry of the University of Oxford in order to work on an empirical ethics research study entitled Psychosis: EIE (Early

Intervention Ethics in Psychosis).[1] The aim of the study was to investigate the conceptualisations of good practice from the point of view of young service users and clinicians in Early Intervention (EI) services for psychosis in England. I then spent more than one year being confronted with the latest results in clinical research on psychotic disorders, ranging from psychosocial to cognitive and neuroscientific approaches to mental illness. At the same time, I designed and performed interviews with clinicians and young service users in EI services in England, investigating the ethical issues involved in the implementation of the early intervention strategy from the perspective of those actors.

The two experiences described above are intertwined. What I learned from both experiences is the extent to which moral concepts are embedded in—and perhaps essential to—the psychiatric context. The *vulnerability* of psychiatric patients and service users, especially young adults, the particular clinician-patient relationship found in psychiatry, marked by the requirements of *trust*, the ethical and legal implications that arise from recent advances in neuroscientific research, as well as their applicability to the mental health context, all require bioethical scrutiny. If a primary scope of bioethical inquiry is to support the implementation of justice in healthcare and to promote people's well-being, then it is vital that mental health be included among the most relevant areas of investigation in bioethics. If there is no health without mental health, I argue, there should be no healthcare ethics without mental health ethics.[2]

In this thesis, I outline some recent developments in the neuroscience and genomics of psychosis and I justify why they require bioethical scrutiny. In order to address the ethical, legal, and social issues raised by these developments, I argue that traditional boundaries among different areas of ethics should be overcome towards an integrated approach, which could situate mental health patients' needs

[1] See Psychosis: EIE webpage in the BeGOOD flagship project website at https://begoodeie.com/psychosis-eie/ last accessed 11 March 2020.

[2] 'No health without mental health' is the title of a policy document published by the Department of Health of the British Government in 2011, see Department of Health, *No Health Without Mental Health: A Cross-Government Mental Health Outcomes Strategy for People of All Ages* (2011). The ambitious goal set up by the Department of Health at that time was to support and implement policy actions that would work towards parity of esteem between mental and physical health services. Indeed, not only was this approach grounded in clinical or health economics considerations but also in the ethical principles of justice, fairness, and promotion of human rights.

at the core of our reflections. I suggest that an empirical investigation of relevant actors' perspectives may help us to identify those needs and address the issues at stake. In this introduction, I first present the background of my research. Then, I outline four research questions I address in the thesis. I then describe the philosophical and legal approach I adopt to answer those questions. Lastly, I provide a summary of the four articles that form the main body of the thesis.

1.1.1 Psychosis and schizophrenia spectrum disorders

Psychosis is an abnormal state of the mind, a set of symptoms characterised by a progressive detachment from reality. Mental disorders that are primarily characterised by psychotic symptoms, such as schizophrenia, are defined as psychotic disorders. According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-5), the schizophrenia spectrum includes schizophrenia, other psychotic disorders, and schizotypal (personality) disorder.[3]

The DSM-5 lists five key features of psychotic disorders, which provide a quick description of psychotic experiences: delusions, hallucinations, disorganised thinking (and speech), grossly disorganised or abnormal motor behaviour (including catatonia), and negative symptoms.[4] Particularly, delusions and hallucinations represent the core features of psychosis. Delusions are defined as:

> [F]ixed beliefs that are not amenable to change in light of conflicting evidence. Their content may include a variety of themes (e.g., persecutory, referential, somatic, religious, grandiose). *Persecutory delusions* (i.e., belief that one is going to be harmed, harassed, and so forth by an individual, organization, or other group) are the most common.[5]

Likewise, hallucinations are defined as:

[3] See American Psychiatric Association, 'Schizophrenia Spectrum and Other Psychotic Disorders', *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (Washington DC: American Psychiatric Association, 2013), 87-122.
[4] Ibid., 87.
[5] Ibid.

> [P]erception-like experiences that occur without an external stimulus. They are vivid and clear, with the full force and impact of normal perceptions, and not under voluntary control. They may occur in any sensory modality, but auditory hallucinations are the most common in schizophrenia and related disorders. Auditory hallucinations are usually experienced as voices, whether familiar or unfamiliar, that are perceived as distinct from the individual's own thoughts.[6]

Delusions and hallucinations, along with disorganised thinking and speech and grossly disorganised motor behaviour (including catatonia) are usually regarded as *positive* psychotic symptoms. On the other hand, *negative* psychotic symptoms include diminished emotional expression, a-volition, anhedonia, and social withdrawal.

It is important to bear in mind that psychosis may result from a wide range of clinical conditions such as traumatic brain injury, brain tumour, depression, Parkinson's and Alzheimer's diseases, as well as non-clinical conditions such as sleep deprivation, substance abuse, alcohol abuse, and medications. In this regard, the diagnosis of a mental disorder in the schizophrenia spectrum is usually defined as a *differential* diagnosis. As reported in the DSM-5, "the diagnosis of a schizophrenia spectrum disorder requires the exclusion of another condition that may give rise to psychosis."[7]

Schizophrenia and other psychotic disorders have a lifetime prevalence of 0.4% to 1% in the general population.[8] Individuals suffering from psychosis and schizophrenia show high levels of comorbidity and functional impairment, leading to a considerable burden for their families and for healthcare systems.[9] Indeed, it has been shown that severe mental illness resulting from chronic psychotic disorders, including schizophrenia, contributes to a significant proportion of the global burden of disease, along with neurological and substance use disorders.

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[6] Ibid.
[7] Ibid., 89.
[8] Bhugra, Dinesh, 'The global prevalence of schizophrenia', *PLoS Med* 2 (5) (2005): e151; quiz e175.
[9] Fusar-Poli, Paolo et al., 'Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis', *Schizophrenia Bulletin* 40 (1) (2014): 120-131.

Taken altogether, mental, neurological, and substance use disorders accounted for 10.4% of global Disability-Adjusted Life Years (DALYs) in 2010, while mental disorders accounted for the largest proportion (56.7%) of DALYs among mental, neurological, and substance use disorders.[10]

In addition, while psychotic disorders affect individuals' general health and well-being over the entire lifespan, the onset of psychotic symptoms is often situated in late adolescence and early adulthood. This fact has led to the recent implementation of EI services for psychosis.[11] Over the past 20 years, the early intervention strategy has been introduced across several healthcare systems in order to promote early diagnosis and treatment for people experiencing a First Episode of Psychosis (FEP), or for those who are defined as being at high-risk or ultra-high-risk of developing a psychotic disorder.[12] EI services were introduced in the UK in 2001 with the publication of the Mental Health Policy Implementation Guide. Established with the aim of reducing the duration of untreated psychosis in order to improve prognosis, promote social recovery, and prevent some of the harms associated with schizophrenia, EI services have started tackling the onset of psychotic symptoms across young and often heterogeneous clinical populations. EI services currently operate by offering a wide range of clinical interventions, including psychosocial intervention, cognitive behavioural therapy, family therapy, and anti-psychotic medications for FEP patients.[13]

Along with the implementation of EI for psychosis, in recent years the development of novel medical technologies has boosted clinical research into the neurobiology of psychotic disorders to an unprecedented scale. While the early intervention strategy is being expanded from psychotic disorders to the full diagnostic spectrum of youth mental health, recent advances in medical technology

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[10] Whiteford, Harvey A. et al., 'The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010', *PLoS ONE* 10 (2) (2015): e0116820.

[11] Yung, Alison R., 'Early intervention in psychosis: evidence, evidence gaps, criticism, and confusion', *Australian and New Zealand Journal of Psychiatry* 46 (1) (2012): 7-9.

[12] For a description of the early intervention strategy for psychosis, see Bird, Victoria et al., 'Early intervention services, cognitive-behavioural therapy and family intervention in early psychosis: systematic review', *British Journal of Psychiatry* 197 (5) (2010): 350-356. With regard to UHR populations, see Fusar-Poli, Paolo et al., 'The psychosis high-risk state: A comprehensive state-of-the-art review', *JAMA Psychiatry* 70 (1) (2013): 107-120.

[13] See Department of Health, *The Mental Health Policy Implementation Guide* (2001).

are reshaping our understanding of the aetiology of mental illness thanks to improved insights in the genetic and neurological aspects of mental conditions.[14]

Ethical, legal, and social issues arise at this intersection of mental health research and psychiatric care. Before I try to identify those ethical concerns, the next section of this introduction will provide an overview of the ongoing implementation of neuroscientific and genomic approaches to psychotic disorders. For the sake of clarity, I will use the term 'psychotic disorders' to refer to all mental disorders in the schizophrenia spectrum, as they are primarily characterised by psychotic symptoms and experiences.

1.1.2 The neurobiology of psychosis: Neuroscience and genomics

Different epistemological models about the nature and the aetiology of mental illness have existed for over a century. The sharp contrast between the biomedical model of mental illness and psychosocial theories of illness aetiology could easily be described as an aetiological fight.[15] I shall say something about the aetiological fight at the beginning of the next section of this chapter. For now, I will accept the assumption that psychotic disorders involve at the same time biological, psychological, and social factors.[16] In clinical services in the United Kingdom, psychotic disorders are usually understood within a *biopsychosocial* framework. While this epistemological assumption continues to drive the implementation of a wide range of clinical interventions, novel diagnostic and risk-assessment tools made possible by neuroscientific and genetic advances could soon be used in the diagnosis and treatment of psychosis.

On the one hand, the widespread use of brain imaging techniques such as structural Magnetic Resonance Imaging (MRI) and functional Magnetic Resonance

[14] For a comprehensive overview of the current state of the art on the neurobiology of psychotic disorders, see the volume edited by Fusar-Poli, Paolo, Borgwardt, Stefan J., and McGuire, Philip (eds.), *Vulnerability to Psychosis. From Neuroscience to Psychopathology* (The Maudsley Series, Hove and New York: Psychology Press, 2012).

[15] See for instance Read, John and Dillon, Jacqui (eds.), *Models of madness. Psychological, social and biological approaches to psychosis* (2nd edn., London & New York: Routledge, 2013); Bentall, Richard P., *Madness Explained. Psychosis and Human Nature* (Penguin Books, 2003).

[16] See Meyer-Lindenberg, Andreas and Tost, Heike, 'Neural mechanisms of social risk for psychiatric disorders', *Nature Neuroscience* 15 (5) (2012): 663-668.

Imaging (fMRI) is shedding light on the neurobiological and neurophysiological correlates of psychotic disorders.[17] By investigating brain structure, function, and physiology, imaging studies have the potential to improve early diagnosis, risk assessment, and to help to develop novel treatments for psychosis and schizophrenia. On the other hand, the increased accessibility of high-throughput and massive parallel DNA sequencing technologies—collectively described as Next-Generation Sequencing (NGS)—is currently boosting the development of psychiatric genomics. As most psychiatric disorders are moderately to highly heritable, large-cohort Genome-Wide Association Studies (GWAS) are currently playing a pivotal role in the investigation of the genomic basis of mental illness, including psychosis and schizophrenia.[18] Furthermore, it is expected that in the near future Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES) will be extensively used in the investigation of susceptibility to major psychiatric disorders.[19]

Neuroscientific research into the neurobiology of psychosis and schizophrenia has been performed for decades.[20] The increased availability and low invasiveness of imaging techniques have contributed to their widespread use in recent years. Imaging techniques currently used to investigate psychosis include molecular imaging such as Positron Emission Tomography (PET), Single-Photon Emission Tomography (SPET), Magnetic Resonance Spectroscopy (MRS), as well as structural (MRI) and functional magnetic resonance imaging (fMRI).[21] Neuroscientific insights from imaging studies are shedding light on a wide range of neurobiological domains: neuroanatomical—including brain structure and volumes—correlates of psychosis and schizophrenia in clinical, high risk, and prodromal populations; and neurophysiological correlates of psychotic experiences, including neurotransmitter dysregulation and abnormal brain areas activation. In

[17] McGuire, Philip et al., 'Functional neuroimaging in schizophrenia: diagnosis and drug discovery', *Trends in Pharmacological Sciences* 29 (2) (2008): 91-98.
[18] Gratten, Jacob et al., 'Large-scale genomics unveils the genetic architecture of psychiatric disorders', *Nature Neuroscience* 17 (6) (2014): 782-790.
[19] See, for instance Homann, O. R. et al., 'Whole-genome sequencing in multiplex families with psychoses reveals mutations in the SHANK2 and SMARCA1 genes segregating with illness', *Molecular Psychiatry* 21 (12) (2016): 1690-1695.
[20] Ross, Christopher A. et al., 'Neurobiology of schizophrenia', *Neuron* 52 (1) (2006): 139-153.
[21] See McGuire et al., *op. cit.*

addition to insights from imaging studies, neurocognitive abnormalities have been shown to predate psychopathology in high-risk subjects.[22]

More specifically, it is important to highlight some relevant findings resulting from the neuroscience of psychotic disorders. First, changes in brain structure and volume, especially with respect to cortical grey matter abnormalities and reduced brain size, have been described both in chronic schizophrenic patients[23] and in prodromal and high-risk subjects.[24] Second, abnormal dopaminergic mechanisms have been shown to play a central role in the development of psychotic symptoms and schizophrenia, leading to the current proposal of the 'dopamine hypothesis of schizophrenia: version III'.[25] Briefly, according to this hypothesis, pre-synaptic striatal dopamine dysregulation is thought to be the final common pathway to psychosis. In addition, dopamine dysregulation is thought to interact with abnormal cortical glutamatergic transmission and the associated NMDA receptors hypofunction (for a clear description of the two interacting 'neurotransmitter' models see Stone, 2012[26] and McGuire et al., 2008, *op. cit.*) in the development of psychotic symptoms and associated grey matter abnormalities observed with disease progression. Third, functional disturbance in the Hypothalamic-Pituitary-Adrenal (HPA) axis and associated high levels of cortisol have been shown to interact with dopaminergic pathways and to characterise transition to psychosis.[27]

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[22] See Pukrop, Ralf and Ruhrmann, Stephan, 'Neurocognitive indicators of high-risk state for psychosis', in Paolo Fusar-Poli, Stefan J. Borgwardt, and Philip McGuire (eds.), *Vulnerability to Psychosis. From Neurosciences to Psychopathology* (Hove and New York: Psychology Press, 2012), 73-94.

[23] Haijma, Sander V. et al., 'Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects', *Schizophrenia Bulletin* 39 (5) (2013): 1129-1138.

[24] Borgwardt, Stefan J. et al., 'Grey matters: Mapping the transition to psychosis', in Paolo Fusar-Poli, Stefan J. Borgwardt, and Philip McGuire (eds.), *Vulnerability to Psychosis. From Neurosciences to Psychopathology*, The Maudsley Series (Hove and New York: Psychology Press, 2012), 95-104.

[25] Howes, Oliver D. and Kapur, Shitij, 'The dopamine hypothesis of schizophrenia: version III--the final common pathway', *Schizophrenia Bulletin* 35 (3) (2009): 549-562.

[26] Stone, James M., 'Glutamate: Gateway to psychosis?', in Paolo Fusar-Poli, Stefan J. Borgwardt, and Philip McGuire (eds.), *Vulnerability to Psychosis. From Neurosciences to Psychopathology*, The Maudsley Series (Hove and New York: Psychology Press, 2012), 117-126.

[27] Day, Fern and Pariante, Carmine, 'Stress and cortisol in the pre-psychotic phases', in Paolo Fusar-Poli, Stefan J. Borgwardt, and Philip McGuire (eds.), *Vulnerability to Psychosis. From Neurosciences to Psychopathology*, The Maudsley Series (Hove and New York: Psychology Press, 2012), 59-72.

Findings from genomics studies are of no less interest. Epidemiological and familial studies have highlighted the strong genetic contribution to the risk of developing schizophrenia and other severe psychiatric disorders. As described above, the advent of low-cost NGS techniques has recently resulted in the GWAS identification of 108 schizophrenia-associated loci that contribute to the risk of developing this common complex disorder.[28] Convergent functional genomics approaches[29] and genetic high-risk studies[30] are proceeding towards the identification of further risk factors and, potentially, genetic risk prediction. Recently, the discovery of increased expression of the C4A gene associated with increased synaptic pruning has been welcomed by the scientific community as a turning point in the attempt to unveil the genetic contribution to disruptive neurophysiological processes leading to schizophrenia.[31] Lastly, WGS and WES exploration of genomic risk factors in schizophrenia has just started identifying genetic mutations segregating with the condition.

To date, diagnosis of a psychotic disorder has usually been performed based on the clinical presentation of psychotic symptoms. Even though little is known of the potential clinical utility of the above research findings, promising attempts in the direction of clinical translation are currently underway. In particular, the search for markers of disease progression could potentially aid diagnosis and benefit treatment options. These include neuroanatomical biomarkers in high-risk populations,[32] blood-based molecular biomarkers for schizophrenia before disease onset,[33] neuro-functional markers in the psychosis prodrome, and especially the integration of different modalities and data sources with machine learning for individual prediction of psychosis transition.[34] In addition, findings into the genetic

[28] Schizophrenia Working Group of the Psychiatric Genomics Consortium, 'Biological insights from 108 schizophrenia-associated genetic loci', *Nature* 511 (7510) (2014): 421-427.
[29] See Ayalew, M. et al., 'Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction', *Molecular Psychiatry* 17 (9) (2012): 887-905.
[30] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[31] Dhindsa, Ryan S. and Goldstein, David B., 'Schizophrenia: From genetics to physiology at last', *Nature* 530 (7589) (2016): 162-163.
[32] Koutsouleris, Nikolaos et al., 'Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers', *Schizophrenia Bulletin* 41 (2) (2015): 471-482.
[33] Chan, M. K. et al., 'Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset', *Translational Psychiatry* 5 (2015): e601.
[34] With regard to the fascinating field of psychosis prediction via machine learning, see for instance Gifford, George et al., 'Using neuroimaging to help predict the onset of psychosis', *NeuroImage* 145

and neurophysiological correlates of psychosis are likely to support drug discovery and development, as well as implement more effective treatment based on profiling individual drug response.[35]

While clinical research on the neurobiology of psychosis as well as translational efforts are proceeding at a fast pace, a *systematic* examination of the ethical and legal issues involved seems to be lacking. Not only do ethical issues that have been described with respect to neuroimaging and genetic research apply—including informed consent, privacy, and confidentiality—but specific concerns arising from the translation of neuroimaging and genomic science into psychiatry must be timely addressed. The present thesis wishes to contribute to the identification of these issues. It tries to answer the following research question: how do we ensure that the introduction of neuroscience and genomics into mental health, and their attempt to unveil the nature and the aetiology of psychosis, are conducted in a way that takes into account the ethical and legal concerns expressed by the scientific community, as well as the dignity, autonomy, and vulnerability of the actors involved? How do we untie the intricate knot of ethical, legal, and social issues at the intersection of mental health research and psychiatric care?

In the next pages, I try to identify those ethical concerns by reviewing the existing ethical and legal literature that interrogates neuroscientific and biomedical approaches to mental illness.

1.1.3 Thesis research question

Technological innovation in biomedicine—what we can call biomedical innovation—results in the translation of novel technologies in psychiatry. Biomedical innovation tackles the neurobiology—that is, the neuroscience and genomics—of psychosis. Brain imaging is used to investigate the neuroscientific correlates of psychosis; next-generation sequencing is used to investigate the genomic basis of psychotic illness. Machine-learning applications are used to analyse data to improve prediction, diagnosis, and treatment. More importantly,

(Pt B) (2017): 209-217; Young, Jonathan, Kempton, Matthew J., and McGuire, Philip, 'Using machine learning to predict outcomes in psychosis', *The Lancet Psychiatry* 3 (10) (2016): 908-909.
[35] See McGuire et al., *op. cit.*

these technologies are currently *converging*. They are and they will increasingly be used together in research and in clinical care. Neurobiological and behavioural data will be used in the future to ameliorate prediction, diagnosis, and treatment of psychotic illness. Biomedical innovation and technological convergence are intertwined in psychiatry.

This thesis tackles biomedical innovation and technological convergence in the particular case of psychosis. It sets out to answer the following research question:

> What ethical issues arise from the convergence of new technologies—that is, brain imaging, next-generation genome sequencing, and machine learning—in tackling psychosis?

And, subsequently:

> What is the most appropriate way to address those issues? How should bioethicists address the ethical issues that arise from technological convergence in the context of psychosis? How can we ensure that technological convergence may truly benefit, and not harm, people who suffer from psychosis?

In this introduction, I first survey the academic literature that provides the ethical and legal background to my investigation. Then, I outline four separate research questions that I answer in the four articles presented in the main body of the thesis. These four questions serve to answer the overarching research question presented above. Then, I outline the philosophical and legal approaches I adopt in the four articles. Lastly, I provide a brief summary of the articles.

1.2 Ethical and legal background

> The mental world in which he had been living was so different from my own that his first-hand testimony alone could convey what it is like to hear

> voices and see visions, to be tormented by waves of unexplained guilt and to lose all sense of the difference between what is imaginary and what is real. Only Henry himself could describe the landscape of this hidden planet on which he lived, along with so many others suffering from schizophrenia.[36]

Along with exciting opportunities for clinical translation, the tremendous advances in the neuroscience and genomics of psychosis described above have the potential to unveil an intricate knot of ethical, legal, and social issues, which must be timely addressed. In this section, I review the existing ethical and legal literature that interrogates the implementation of neurobiological approaches to psychosis and schizophrenia.

Before focusing on ethical and legal concerns, it is important to highlight that the recent implementation of neurobiological approaches to psychosis is explicitly situated within an epistemological framework that understands mental illness primarily in a biomedical manner. However, as portrayed by the wide range of clinical interventions offered by early intervention and community mental health services in the UK,[37] as well as by the coexistence within the services of a variety of clinical specialisations, mental illness can be understood in an epistemological continuum which ranges from psychosocial to cognitive, neuropsychiatric, and neuroscientific approaches.

On one extreme of this spectrum, social approaches to mental illness have traditionally refused to accept the biomedical model of psychosis. The position put forward by these epistemological approaches, which during the second half of the 20th century contributed to the establishment of the anti-psychiatry movement,[38] is best represented in the seminal book *The Myth of Mental Illness* by Thomas S. Szasz.[39] Although rejecting any affiliation with the anti-psychiatry movement

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[36] Cockburn, Patrick and Cockburn, Henry, *Henry's Demons. A Father and Son's Journey Out of Madness* (London: Simon & Schuster, 2011), xiv.

[37] These include, for instance, psychosocial interventions, family and occupational therapy, mindfulness techniques, Cognitive Behavioural Therapy (CBT), and antipsychotic medications.

[38] See, for instance, Laing, Ronald D., *The Politics of Experience and The Bird of Paradise* (New York: Penguin Books, 1990/1967).

[39] Szasz, Thomas S., *The Myth of Mental Illness. Foundations of a Theory of Personal Conduct*, Perennial (New York: HarperCollins, 2010/1974).

throughout his career, Szasz argued in favour of a complete refusal of the biomedical model of mental illness. As he wrote:

> My aim in this essay is to raise the question 'Is there such a thing as mental illness?' And to argue that there is not. […] Everything I read, observed and learned supported my adolescent impression that the behaviours we call "mental illness" and to which we attach the hundreds of derogatory labels in our lexicon of lunacy are not medical diseases. They are the products of the medicalization of disturbing or disturbed behaviours – that is, *of the observer's construction and definition of the behaviour of the persons he observes as medically disabled individuals needing medical treatment*. This cultural transformation is driven mainly by the modern therapeutic ideology that has replaced the old theological worldview, and the political and professional interests it sets in motion.[40]

On the opposite side of the epistemological spectrum, recent innovations in medical technology and the expansion of clinical neurosciences have resulted in the current emphasis on neuroscientific and biomedical approaches to mental illness. An example of this second approach is provided by Thomas R. Insel, former director of the US National Institute of Mental Health, who declared in his 'strategic plan for research on mental illness':

> Herein, I will distill these to 4 opportunities that can transform our approach to mental illness. First, we can understand mental disorders as brain disorders, that is, disorders of specific brain circuits. […] Second, we can understand mental disorders as developmental brain disorders […] we will need a new strategic approach that ensures bringing the best tools of genomics and neurosciences to solve the tough questions of pathophysiology of mental disorders as well as innovative behavioural science to get new, effective treatments into the hands of clinicians.[41]

[40] Ibid., ix, xvii.
[41] Insel, Thomas R., 'Translating scientific opportunity into public health impact: a strategic plan for research on mental illness', *Archives of General Psychiatry* 66 (2) (2009): 128-133: 130-132.

In this thesis, I do not take a stance on the aetiological fight between psychosocial and biomedical approaches to psychosis. This thesis does *not* aim to establish who is right and who is wrong in this century-long dispute. In a sense, my thesis is an exercise of aetiological neutrality. I remain neutral in the fight between psychosocial and biomedical theories of mental illness. Adopting such aetiological neutrality is instrumental to the aim of my work, which is to investigate the potential benefits as well as the moral challenges that arise from the convergence of neuroscience and genomics in tackling psychotic illness. More precisely, psychotic illness has been shown to include biological, psychological, and social factors. In this thesis, I begin with the assumption that a *biopsychosocial* approach to psychosis is the most suitable to the scope of my analysis. A biopsychosocial approach to psychosis recognises the genetic contribution to disrupted neurophysiological processes leading to psychotic experiences, as well as the relevance of psychological and social factors for illness onset in at risk individuals, such as early childhood trauma, urban upbringing, and drug abuse. Such an approach constitutes the basis of the present analysis.[42]

Nonetheless, a thorough ethical analysis must recognise the existence of several models about the aetiology of psychosis, which have characterised the scientific debate over the past decades. These tensions must be acknowledged against the identification of ethical and legal issues involved in the implementation of novel neurobiological approaches to mental illness. Particularly, tensions across the epistemological spectrum are relevant for the discussion of how moral challenges are perceived by different stakeholders, such as researchers, mental health professionals, and informal caregivers. Such differences have been acknowledged and investigated in the empirical component of my doctoral research, and results are presented in Article two and Article three.

[42] See Meyer-Lindenberg and Tost, *op. cit.* For a review of the implications of the *biopsychosocial* model for the definition of mental illness, see Engel, George L., 'The need for a new medical model: a challenge for biomedicine', *Science* 196 (4286) (1977): 129-136.

1.2.1 Ethical, legal, and social issues

The development of novel neurobiological approaches to psychosis and schizophrenia is exceptionally situated at the interface of several ethics domains. In recent years, the bioethics debate has focused on the identification of a large number of Ethical, Legal, and Social Issues (hereafter, ELSI) related to advances in genomics[43] and neuroscience.[44] The issues identified within the two domains are often related, though a certain degree of specificity for each domain—be it genomics or neuroscience—is constantly maintained by scholars working in ELSI research. These issues include for instance: return of results, management of Incidental Finding (IFs), lack of immediate clinical utility, research governance, data management, privacy and confidentiality.[45]

The implementation of neuroscientific and genomic approaches to mental illness questions at the same time neuroethics, the ethics and regulation of genomics, research ethics, and clinical ethics. More precisely, it questions these different domains of ethico-legal scholarships and, at the same time, it prompts us to reflect on their boundaries and interconnections. Nonetheless, the development of the novel neurobiological approaches to psychosis described above situates 'traditional' ELSI of neuroscience and genomics within the domain of psychiatric ethics.[46] Given the nature of psychiatric care, advances in medical technologies are likely to affect the identity and agency of research participants and clinical populations. Particularly, risks of stigmatisation, labelling, and potential over-diagnosis are peculiar, although not unique, of the mental health domain and must be carefully assessed both in the conduct of clinical research and in translational efforts.[47]

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[43] See Howard, H. C. et al., 'The Ethical Introduction of Genome-Based Information and Technologies into Public Health', *Public Health Genomics* 16 (3) (2013): 100-109.
[44] See, for instance, the anthology edited by Illes, Judy and Sahakian, Barbara J. (eds.), *Oxford Handbook of Neuroethics* (Oxford University Press, 2011).
[45] See Kaye, Jane, 'The Tension Between Data Sharing and the Protection of Privacy in Genomics Research', *Annual Review of Genomics and Human Genetics* 13 (1) (2012): 415-431.
[46] Sadler, John Z., Van Staden, Werdie, and Fulford, Kenneth William Musgrave (eds.), *Oxford Handbook of Psychiatric Ethics* (Oxford: Oxford University Press, 2015).
[47] For an interesting description of the risk of stigma at the interface of clinical research and psychiatric care in the context of psychosis, see Yang, Lawrence H. et al., 'Stigma in early stages of psychotic illness: Connections with cognitive neuroscience', in Paolo Fusar-Poli, Stefan J.

In order to reconstruct the ELSI that arise from the current implementation of neurobiological approaches to psychotic disorders it is essential to make three important specifications.

First, ethical issues arise from the two separate domains of *neuroscience* and *genomics* of mental illness. In the case of psychotic disorders, these two domains are inherently intertwined. This is the reason why, in this thesis, I collectively describe neuroscientific and genomics approaches as *neurobiological* approaches to mental illness. I investigate the ethical issues that arise from recent efforts in tackling the *neurobiology* of psychosis. More precisely, I investigate the ethical issues arising from the convergence of neuroscience and genomics in tackling psychotic illness.[48] I explore the idea of technological convergence in research and clinical approaches to psychosis in Article one of this thesis—and, to a certain extent, in the other three articles that constitute the main body of the thesis. As specified above, ELSI arising from the neuroscience and genomics of psychosis are often related, though they maintain a degree of specificity given the diverse modalities of scientific investigation. The intersection and convergence of neuroscience and genomics is indeed peculiar to the neuropsychiatry domain. This is the object of the present investigation.

Second, specific ELSI arise within clinical *research* as well as in translational efforts into psychiatric *practice*. It is important to highlight that neurobiological insights on psychosis have been, to date, mainly confined to clinical research. Even though translational efforts are underway, the clinical utility of the findings previously described has been, to date, very limited. As the lack of immediate clinical utility represents an ethical issue *per se*, a proactive approach mandates that ethical and legal issues in clinical translation be identified while this very translation is still underway. I expand on this principle in Article one.

Borgwardt, and Philip McGuire (eds.), *Vulnerability to Psychosis. From Neurosciences to Psychopathology*, The Maudsley Series (Hove and New York: Psychology Press, 2012), 159-176.

[48] On the convergence of neuroscientific and genomic approaches to psychosis see the interesting volume recently edited by Thompson, Andrew D. and Broome, Matthew R. (eds.), *Risk Factors for Psychosis. Paradigms, Mechanisms, and Prevention* (Academic Press, 2020). In this book, I contributed a chapter which is not included in my thesis, see Corsico, Paolo and Singh, Ilina, 'The ethics of identifying and treating psychosis risk', in Andrew D. Thompson and Matthew R. Broome (eds.), *Risk Factors for Psychosis. Paradigms, Mechanisms, and Prevention* (Academic Press, 2020), 335-350.

Nonetheless, ELSI arising in clinical research on the neurobiology of psychotic disorders and ELSI arising from the clinical translation of research findings remain deeply intertwined, though they are distinguishable by referring to the different needs of clinical and research populations.

Third, the implementation in the United Kingdom of the early intervention strategy, which is designed to support the provision of community mental health care and to promote early diagnosis and treatment, has resulted in an emphasis on targeting young populations both in research and in clinical care. Young people experiencing early signs of psychosis or the early phases of a psychotic disorder constitute the target population of early intervention services. At the same time, these individuals are often recruited in research programmes investigating the neurobiology of psychosis and schizophrenia.[49] For this reason, ethical, legal, and social concerns refer primarily—though not entirely—to young people, adding a further layer of vulnerability to already particularly vulnerable individuals: that of the young age.

1.2.2 The (neuro) ethics of brain imaging in psychiatry

Over the past decades, the development of cognitive neurosciences has resulted in the establishment of neuroethics as an independent field of ethical inquiry.[50] Traditionally, neuroethics has focused on the so-called 'ethics of neuroscience'—meaning the ethical issues arising from neuroscience as a field of scientific investigation—as well on the 'neuroscience of ethics', meaning the neurobiological bases of moral reasoning and their implications for common ethical concepts such as agency, autonomy, and personal identity. The implementation of neurobiological approaches to psychotic disorders intersects the neuroethics debate mainly in the first sense, that is, the ethical issues arising from the expansion of neurosciences into psychiatry.

[49] See, for instance Fusar-Poli, P. et al., 'Outreach and support in south London (OASIS), 2001-2011: Ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis', *European Psychiatry* 28 (5) (2013): 315-326.
[50] See Illes and Sahakian (eds.), *op. cit.*

More specifically, neuroscientific approaches to psychotic disorders raise a number of ethical concerns that can be broadly summarised under two main categories. On the one hand, ethical issues arise from the introduction of *imaging research* in psychiatry, which usually involves vulnerable clinical populations. On the other hand, the expansion of neuroimaging in psychiatry has a broader impact at the individual and social level, being associated with issues such as neuro-essentialism, stigma, as well as potentially unsound applications in forensic psychiatry. Bluhm et al. have provided a very useful summary of the ethical issues that have been associated with brain imaging in psychiatry, analysing the potential implications of brain imaging for screening, prediction, and diagnosis of psychiatric disorders, as well as potential implications in forensic psychiatry.[51]

With regard to the ethical issues arising from imaging *research*, Racine and Illes have compiled a list of recommendations that can serve as a 'research ethics landscape' also for the introduction of neuroimaging research in psychiatry.[52] The authors list the following areas of ethical concern: incidental findings and informed consent, privacy, recruitment practices and confidentiality, decisional capacity and vulnerable populations, stigma and discrimination, scientific value, conflict of interest, and transfer of knowledge. Among the areas identified by Racine and Illes, the management of IFs has probably been the most explored within neuroethics, as the moral dilemma of whether researchers have a duty to disclose incidental findings to participants represents a major challenge to bioethics and health law. As Susan Wolf writes, "[m]erely asking this question is a profound challenge to the structure of bioethics and health law. Both fields approach the world of research and the world of medical care very differently. The problem of incidental findings challenges this traditional dichotomy."[53] In addition, other scholars such as

[51] Bluhm, Robyn et al., 'Ethical Issues in Brain Imaging in Psychiatry', in John Z. Sadler, Werdie van Staden, and Kenneth William Musgrave Fulford (eds.), *Oxford Handbook of Psychiatric Ethics*, 2 (Oxford: Oxford University Press, 2015), 1109-1126. See also the very interesting paper by Boyce, Alison C., 'Neuroimaging in psychiatry: evaluating the ethical consequences for patient care', *Bioethics* 23 (6) (2009): 349-359.

[52] Racine, Eric and Illes, Judy, 'Emerging ethical challenges in advanced neuroimaging research: review, recommendations and research agenda', *Journal of Empirical Research on Human Research Ethics* 2 (2) (2007): 1-10.

[53] Wolf, Susan M., 'Incidental findings in neuroscience research: a fundamental challenge to the structure of bioethics and health law', in Judy Illes and Barbara J. Sahakian (eds.), *The Oxford Handbook of Neuroethics* (Oxford: Oxford University Press, 2011), 623-634, 624.

Robinson et al. have highlighted how ethical issues in imaging research are even more complex in the case of psychosis and psychopathy than in traditional imaging research.[54]

On the other hand, scholars have been apprehensive of the implications that the introduction of brain imaging in psychiatry may have on a *broader* societal level, such as neuro-essentialism, stigma associated with mental illness, and potential imaging applications in forensic psychiatry. Particularly, the issue of neuro-essentialism falls deeply within the domain of neuroethics. Broadly defined, neuro-essentialism (along with its genetic counterpart, genetic essentialism) is a form of determinism, according to which all human behaviour is determined by neural circuits, leaving—in theory—little or no room for freedom, autonomy, and agency.[55] The issues as to whether neuro-essentialist thinking may characterise the introduction of brain imaging for psychotic disorders at a societal level, and to what extent neuro-essentialist thinking may influence social stigma attached to mental illness remain crucial for the development of psychiatric ethics and neuroethics, and are therefore central to the present analysis.[56]

1.2.3 The ethics of psychiatric genomics

The ethics of genomics represents one of the most explored—if not the most explored—areas of bioethical inquiry.[57] It is beyond the scope of this work to summarise the ethical issues embedded in the development of genomic science. Nonetheless, it is important to specify how the ethics of genomics intersects clinical research and translation efforts into the neurobiology of psychosis.

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[54] Robinson, Louise, Sprooten, Emma, and Lawrie, Stephen M., 'Brain imaging in psychosis and psychopathy--ethical considerations', *Cortex* 47 (10) (2011): 1236-1239.

[55] A comprehensive account of neuro-essentialist theories is provided by Reiner, Peter B., 'The rise of neuroessentialism', in Judy Illes and Barbara J. Sahakian (eds.), *The Oxford Handbook of Neuroethics* (Oxford: Oxford University Press, 2011), 161-175.

[56] For the impact of neuroimaging on stigma in psychiatry—though focused on depression rather than psychosis—see the fascinating study by Illes, J. et al., 'In the mind's eye: provider and patient attitudes on functional brain imaging', *Journal of Psychiatric Research* 43 (2) (2008): 107-114.

[57] See, for instance, the comprehensive anthology edited by Chadwick, Ruth (ed.), *The Concise Encyclopedia of the Ethics of New Technologies* (Academic Press, 2001).

In 1998, the Nuffield Council on Bioethics published a document entitled *Mental Disorders and Genetics: The Ethical Context*.[58] Although being not up to date with respect to its scientific background, this document remains an invaluable source for the identification of the ELSI that arise in psychiatric genomics. Different aetiological models and clinical applications, potential future genetic testing procedures (including possible Direct-To-Consumer developments), risk prediction and risk communication, links with the reproductive domain, risks of labelling, stigma, and discrimination as well as ethical issues in psychiatric genomic research are all extensively described in the document. Many of these issues remain deeply intertwined with those identified in the neuroethics debate. Particularly, potential risks are weighed in the document against the potential benefits of more accurate diagnostic and prognostic measures.

Even though the document remains an invaluable source of ethical reflection, recent developments in the field of psychiatric genomics are, nonetheless, worth considering. Kong et al. have provided an interesting update on the ethical agenda at the intersection of psychiatric genomics, mental health treatment, and public health. As they write:

> [T]he discourse of empowerment and participation in genomic medicine raises two key ethical issues when applied to treating mental disorders. First, how personal, genetic responsibility is framed requires closer scrutiny, particularly as it could potentially undermine psychosocial therapeutic approaches and the clinician-patient therapeutic alliance […]. Second, the application of genomics to broader public health interventions risks shifting attention away from critical analyses of ways in which inequitable socio-economic, political and cultural structures can directly impact on mental health care.[59]

[58] Nuffield Council on Bioethics, *Mental Disorders and Genetics: The Ethical Context* (London, 1998).
[59] Kong, Camillia, Dunn, Michael, and Parker, Michael, 'Psychiatric Genomics and Mental Health Treatment: Setting the Ethical Agenda', *The American Journal of Bioethics* 17 (4) (2017): 3-12: 6.

Kong et al. seem to suggest that the *scale* of recent advances in psychiatric genomics has broader implications on how our societies frame individual responsibility and understand social relationships, particularly in (mental) health care. The authors' warnings retain their strength when we consider that most of the renewed interest into the genomics of psychotic disorders comes from the recent implementation of next-generation sequencing techniques along with GWAS, WGS, and WES studies, as outlined in previous sections of this introduction.

As with other forms of NGS-based research and clinical applications, the implementation of large-cohort, NGS-based clinical research on the genomics of psychosis must undergo a thorough ethical and legal scrutiny.[60] Therefore, it is important to highlight how, along with traditional ethical concerns in psychiatric genomics, the ethics debate has recently been focusing on the impact of NGS technologies on psychiatric genomics and mental health.[61] The latter developments are the most relevant in the context of the present research.

1.2.4 Psychiatric ethics

Ethical, legal, and social issues arise from the development of neuroscience and genomics. However, the fact that these biomedical approaches are used to investigate the neurobiology of psychosis situates the ELSI previously described within the domain of *psychiatric ethics*.

This may seem obvious. However, situating the present research within the realm of psychiatric ethics is essential for two reasons. First, it provides the theoretical context necessary to assess the impact of ethical concerns usually found in psychiatry, such as stigma, labelling, and impact on patients' identity and agency. Second, it contextualises my theoretical framework within the web of relationships

[60] With regard to the ELSI of NGS-based applications see Clarke, Angus J., 'Managing the ethical challenges of next-generation sequencing in genomic medicine', *British Medical Bulletin* 111 (1) (2014): 17-30. See also Pinxten, Wim and Howard, Heidi C., 'Ethical issues raised by whole genome sequencing', *Best Practice & Research Clinical Gastroenterology* 28 (2) (2014): 269-279.

[61] See for instance Biesecker, Barbara B. and Peay, Holly L., 'Genomic sequencing for psychiatric disorders: promise and challenge', *International Journal of Neuropsychopharmacology* 16 (7) (2013): 1667-1672. See also Hoge, Steven K. and Appelbaum, Paul S., 'Ethics and neuropsychiatric genetics: a review of major issues', *International Journal of Neuropsychopharmacology* 15 (10) (2012): 1547-1557.

among different stakeholders—such as patients, families, social workers, psychologists, and psychiatrists—in mental health care. This web of relationships is characterised by completely different dynamics than the ones found in physical health care. In this regard, psychiatric ethics can *also* be understood as a specialisation of clinical ethics, which is marked by a specific, and peculiar, set of relationships and values at stake.

As in the case of neuroethics, psychiatric ethics has emerged as an independent field of ethical investigation during the past decades.[62] Again, it is beyond the scope of this work to summarise the overall development of psychiatric ethics. Nonetheless, it is important to identify those theoretical insights from psychiatric ethics that may help us to frame an ethics of psychiatry as it intercepts current advances in neuroscience and genomics. First, as stigma, labelling, and genetic and neuro-essentialism may result from the introduction of neuroscience and genomics into mental health, insights from psychiatric ethics remind us of how these social occurrences are dependent on historical developments and cultural contexts. As Haslam writes:

> Psychiatric stigma is multifaceted, but its primary dimensions include social distance (the desire not to interact with people experiencing mental disorders), perceived dangerousness (the perception that people with mental disorders are uncontrollable and violent), pessimism (the belief that people with mental disorders are unlikely to overcome them), and blame (the judgement that people with mental disorders are morally responsible for their deviant behaviour and experience).[63]

Second, the field of psychiatric ethics reminds us of the particular declination that ethical principles and values traditionally investigated in bioethics, such as autonomy, beneficence, and care must undergo when translated in the mental health

[62] See Bloch, Sidney and Chodoff, Paul, *Psychiatric Ethics* (New York: Oxford University Press, 1981). See also the massive two-volume *Oxford Handbook of Psychiatric Ethics* edited by Sadler, Van Staden, and Fulford (eds.), *op. cit.* This handbook provides an interesting overview of the psychiatric ethics literature.
[63] Haslam, Nick, 'Genetic essentialism, neuroessentialism, and stigma: commentary on Dar-Nimrod and Heine (2011)', *Psychological Bulletin* 137 (5) (2011): 819-824: 820.

context. This is particularly evident with reference to philosophical approaches with a longstanding tradition in bioethics, such as principlism, utilitarianism, and virtue theory.[64] In discussing a *value-based* approach to psychiatric ethics, John Sadler, for instance, has advocated for a pragmatic translation of ethical values in the psychiatric context. Sadler argues that there are theoretical and practical challenges to using philosophical ethics as a method in psychiatric ethics. According to him, traditional philosophical ethics is ill suited to solve ethical challenges in psychiatric practice.[65] I do not adopt a value-based approach in this thesis. However, I believe that the value-based approach developed by Sadler critically highlights the importance of an appropriate translation of moral values and ethical principles in the psychiatric context. As Sadler writes, "Psychiatric ethics is action-oriented, requires a concrete translation of values among a group of stakeholders, and must negotiate values from a variety of viewpoints and assumptions, as opposed to philosophical ethics".[66]

1.2.5 Sources of the law: Three important specifications

In the next pages, I identify the sources of the law that are relevant to my thesis. Before I do that, I must make three important specifications.

First, my fieldwork took place in England. Most of my legal inquiry refers to the United Kingdom, more specifically to the jurisdiction of England and Wales. Therefore, the legal reflections presented in this thesis refer—mostly—to this jurisdiction. When I was first enrolled as a doctoral student in September 2016, the United Kingdom was a member State of the European Union (EU). At the time of writing—August 2020—the United Kingdom is no longer a member State of the EU, having left the Union through the process known as 'Brexit' on 31 January 2020. The United Kingdom is presently in the so-called 'transition period' during which EU legislation continues to be valid. The transition period is expected to last

[64] See section IV of the *Oxford Handbook of Psychiatric Ethics* in Sadler, Van Staden, and Fulford (eds.), *op. cit.*, 267-492.
[65] Sadler, John Z., 'Value-Based Psychiatric Ethics', in John Z. Sadler, Werdie Van Staden, and Kenneth William Musgrave Fulford (eds.), *The Oxford Handbook of Psychiatric Ethics* (Oxford: Oxford University Press, 2015), 474-492.
[66] Sadler, Van Staden, and Fulford (eds.), *op. cit.*, xxxvi.

until 31 December 2020. European legislation remains for now an applicable source of regulatory oversight in England and Wales. It is not possible to know exactly what the consequences of Brexit will be for medical law in England and Wales. After the implementation period, some EU legislation will remain enforceable in England and Wales, while others will not.[67] I hope that the reader will bear in mind this situation when assessing the validity of the legal claims contained in this work.

Second, legal issues arising from neurobiological approaches to psychosis are intertwined with ethical issues, as I have tried to demonstrate in the last pages. It would be artificial to separate the two domains. This principle will be more evident in Articles two and three of the thesis, where I describe the results of the qualitative research I conducted for my fieldwork. As relevant stakeholders in mental health care seem to endorse, ethical and legal issues in psychiatry are inherently intertwined.

Third, as I describe later in this introduction, Article four of the thesis investigates the legal challenges that arise from the use of *machine learning* for psychosis prediction. Machine learning methods for psychosis prediction—used across several data sources including neuroimaging, genetic, cognitive, and behavioural data—have emerged in the last years as one of the most interesting avenues for the clinical translation of neurobiological findings.[68] Most sources of law that I describe here are relevant primarily—though not exclusively—in relation to Article four, as this represents the 'most purely legal' article in the thesis.

Bearing in mind these three specifications, I can identify relevant sources of law as belonging to two areas: (i) clinical research regulation and data protection, and (ii) mental health law as it regulates the provision of mental health care in England and Wales. Whereas clinical research regulation and data protection primarily—though not exclusively—apply to the introduction of neuroscience and genomics into clinical *research*, mental health law applies mainly to translational efforts into clinical *care*.

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[67] For some general guidance on this issue, see the UK government website at https://www.legislation.gov.uk/eu-legislation-and-uk-law, last accessed 9 March 2020.

[68] In this regard, see the useful review provided by Shatte, Adrian B. R., Hutchinson, Delyse M., and Teague, Samantha J., 'Machine learning in mental health: a scoping review of methods and applications', *Psychological Medicine* 49 (9) (2019): 1426-1448.

1.2.6 Clinical research regulation and data protection

I hope that I will not compromise the reader's faith in the theoretical soundness of this work by declaring that it is not easy, for a European student, to unfold the complexities of medical and mental health law in England and Wales. An invaluable source in this task is the work of Margaret Brazier and Emma Cave, *Medicine, patients and the law*,[69] even though it does not cover mental health law in depth.

A number of international documents have influenced how clinical research is regulated in the United Kingdom. A general legal framework for medical legislation in Europe is provided by the European Convention on Human Rights (ECHR),[70] which was rendered directly enforceable in the domestic courts in the United Kingdom by the Human Rights Act 1998. Both the ECHR and the Human Rights Act 1998 have historically influenced how medical law and clinical research regulation are shaped in England and Wales. Again, on a general level, an invaluable source of regulatory oversight is provided by the so-called Oviedo Convention on Human Rights and Biomedicine,[71] its additional protocol concerning biomedical research of 2005,[72] and the additional protocol concerning genetic testing for health purposes of 2008.[73] However, it is important to remember that the Oviedo Convention has not been ratified by the United Kingdom. Therefore, it is not directly enforceable in England and Wales, though its principles continue to shape the EU regulatory framework. Specifically with regard to the conduct of clinical research, ethical principles have been established by the World Medical Association in the Declaration of Helsinki,[74] which sets out the standards

[69] Brazier, Margaret and Cave, Emma, *Medicine, patients and the law* [VI edition] (Manchester: Manchester University Press, 2016). See especially chapter 4 'A Relationship of Trust and Confidence', chapter 6 'Capacity, Consent and Compulsion', and chapter 15 'Healthcare Research'.
[70] Council of Europe and European Court of Human Rights, Convention for the Protection of Human Rights and Fundamental Freedoms, [1950].
[71] Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine [1997].
[72] Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research [2005].
[73] Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Genetic Testing for Health Purposes [2008].
[74] World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects [1964], VII revision 2013.

that national legislations must meet in order to ensure the ethically sound conduct of medical research.

Health research governance in England and Wales is the responsibility of the Health Research Authority (HRA). In 2017 the HRA and the four UK Health Departments published the UK Policy Framework for Health and Social Care Research. This document sets out principles, roles, and responsibilities for the conduct of clinical research in these jurisdictions. It also provides a comprehensive account of the applicable statutes in each jurisdiction.[75] The conduct of clinical trials in England and Wales is subject to The Medicines for Human Use (Clinical Trials) Regulations 2004. The 2004 Regulations may soon be amended in light of the new EU Clinical Trials Regulation 536/2014.[76] Even though it was published in 2014, the new EU regulation will only become operative after the development of a fully functional EU clinical trials portal. It will thus not have direct application in the UK, since the UK has now left the EU.

Given the issues of data management and data protection arising from neuroscientific and genomic applications, some specific sources of legislation are then relevant for this thesis. Kaye et al. have provided a very useful account of the current legal position in the UK with regard to the access to genomic information.[77] Their account includes the Freedom of Information Act 2000 and the Data Protection Act 1998. Further, the most important legal instrument with regard to data management and data protection in the EU is currently the General Data Protection Regulation 2016/679 (GDPR).[78] The GDPR became enforceable in the EU on 25 May 2018. On that date, the UK was still a member State of the EU. After the GDPR became enforceable in the UK, the UK Parliament promulgated the Data Protection Act 2018, which substituted the Data Protection Act 1998 and complemented the GDPR with additional domestic legal provisions.

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[75] See Health Research Authority and the four UK Health Departments, UK Policy Framework for Health and Social Care Research [2017], 33-6.

[76] EU Regulation 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [2014] OJ L158/1.

[77] Kaye, Jane et al., 'Can I access my personal genome? The current legal position in the UK', *Medical Law Review* 22 (1) (2014): 64-86.

[78] EU Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) [2016] OJ L119/1.

1.2.7 Mental health law (in England and Wales)

The conduct of health care research and the provision of mental health care in England and Wales are subject to specific statutes. Over the last decades, mental health law has followed a peculiar historical development in England and Wales. An invaluable source of knowledge in navigating mental health law in this jurisdiction is provided by Peter Bartlett and Ralph Sandland in their manual *Mental Health Law: Policy and Practice*.[79]

English mental health legislation is relevant to this thesis for three reasons: (i) it establishes principles and rules on the issue of *mental capacity* to take part in research and to consent to clinical care; (ii) it regulates the provision of mental health care by establishing principles regarding the assessment and treatment of people who suffer from a mental disorder; (iii) it defines rules for the involuntary hospitalisation and coercive treatment of those who suffer from a mental disorder and are at risk of harm to self or others. Mental health law is regulated by two key statutes in England and Wales: the Mental Health Act 1983 (as amended by the Mental Health Act 2007) and the Mental Capacity Act 2005. Compulsory hospital admission for assessment or treatment of the mentally ill, community treatment orders, detention and criminal commitment, mental capacity to consent to research and care are all covered by the two Acts. The UK government has provided useful guidance for the application of the two Acts by publishing Codes of Practice for the Mental Health Act 1983[80] and for the Mental Capacity Act 2005.[81]

Lastly, the development of machine-learning applications for risk assessment, diagnosis, and prediction in the context of psychosis are the subject of Article four of this thesis. As I argue in this article, the use of prediction tools in psychiatry interacts with how risk, benefit, and harm are interpreted in mental health law. Relevant case law from UK Courts and from the European Court of Human Rights is cited and analysed in Article four.

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[79] Bartlett, Peter and Sandland, Ralph, *Mental Health Law: Policy and Practice* [IV edition] (Oxford: Oxford University Press, 2014).
[80] Department of Health, *Mental Health Act 1983: Code of Practice* (2015).
[81] Department for Constitutional Affairs, *Mental Capacity Act 2005 Code of Practice* (2007).

1.3 Research questions

The development of neurobiological approaches to psychosis and schizophrenia is exceptionally situated at the interface of several ethics domains. As I described above, recent advances in neuroscience and genomics unveil an intricate knot of ethical, legal, and social issues, both in clinical research and in the clinical translation of research findings. In this thesis I try to answer the following general research question: How should bioethicists address the ethical issues that arise from technological convergence in the context of psychosis? How can we ensure that technological convergence may truly benefit, and not harm, people who suffer from psychotic illness?

As I argue in the thesis, and particularly in Article one, answering this question requires a collaborative effort by scholars working in different branches of ethics. My thesis aims to contribute to this effort by answering four narrower research questions. Each of the articles that form the body of the thesis is dedicated to answering one of these four questions. First, in Article one I answer a theoretical research question:

1. How should we untie the intricate knot of ethical, legal and social issues at the intersection of mental health research and psychiatric care? How do we build a theoretical framework that can support the ethical implementation of novel neurobiological approaches to psychotic disorders, in clinical research and psychiatric care?

The coexistence of a high number of ethical concerns as well as different theoretical approaches sheds light on the research gap I intend to fill. Traditional boundaries among different areas of ethics have served the purpose of *specialisation*, as much as they have allowed scholars to tackle ethical issues at a very detailed level. However, the developments in medical technology that constitute the object of this research lay at the *interface* of several ethics domains. At this interface, one can only find patients, professionals, and carers, their concerns and the values at stake.

Thus, the definition of an *integrated* ethical framework constitutes the basis of Article one. Here I argue that traditional boundaries among different areas of ethics research should be overcome towards an integrated approach that could situate mental health patients and service users' needs at the core of our reflections.

In Articles two and three I then answer two empirical research questions. As I explain in more detail later in this introduction, my work is committed to the empirical turn in bioethics.[82] In Articles two and three I present the results of an empirical ethics study based on qualitative research methods that I conducted with Greater Manchester Mental Health NHS Foundation Trust and in several universities in England. The research study was entitled ELSI-NAPS (Ethical, Legal and Social Issues in Novel Neurobiological Approaches to Psychosis and Schizophrenia: A qualitative study). In Article two, I answer the following research question:

2. How do different stakeholders—in this case researchers and mental health professionals—conceptualise and respond to the ELSI related to the implementation of novel neurobiological approaches to psychosis? How do they frame the ethical anchors of their professional role? More precisely, drawing from the results of the ELSI-NAPS study, in this article I answer the question: how do researchers and mental health professionals conceptualise the moral challenges of accessing neurobiological information in the context of psychosis?

Article two presents findings from individual semi-structured interviews I conducted with 14 researchers in mental health and 14 mental health professionals. I investigated their views through open questions, prompting, and probing. The article compares results in the two groups and presents reflections that may inform ethico-legal scholarship. In Article three, I answer the following research question:

[82] See Borry, Pascal, Schotsmans, Paul, and Dierickx, Kris, 'The Birth of the Empirical Turn in Bioethics', *Bioethics* 19 (1) (2005): 49-71.

3. How do carers of someone suffering from psychosis conceptualise and respond to the ELSI related to the implementation of novel neurobiological approaches to psychosis? How do they frame the ethical anchors of their *social* role? More precisely, drawing from the results of the ELSI-NAPS study, in this article I answer the question: what moral challenges do carers recognise as most problematic in the introduction of neuroscience and genomics into psychiatry? How can the implementation of novel neurobiological approaches to psychosis be beneficial to patients and families, according to carers?

Article three presents findings from three focus groups I conducted with 15 carers of a patient or service user suffering from a psychotic disorder. I investigated carers' views and shared social norms through open questions, group discussion, and participant interaction.

Lastly, Article four tackles a legal question. One of the most promising avenues for the clinical translation of neurobiological findings is the field of psychosis prediction. The field of psychosis prediction is being revolutionised by the use of *machine learning* and narrow artificial intelligence across several data sources, including neuroimaging, genetic, and behavioural data. The use of machine learning for psychosis prediction poses specific legal questions. In Article four, I thus answer the following research question:

4. How should we regulate the use of machine learning for psychosis prediction in clinical research and in the practice of psychiatry? What legal challenges arise from the use of machine learning for psychosis prediction across several data sources, with reference to the jurisdiction of England and Wales?

In the next pages I outline the philosophical and legal approach from which I try to answer the above four research questions.

1.4 Philosophical and legal approach

Normative approaches to bioethics have traditionally focused on the justification of moral principles, rules, and obligations, which in turn serve as a foundation for different sets of moral norms. Normative approaches with a longstanding tradition in bioethics include consequentialist theories such as *act* and *rule* utilitarianism, deontological theories such as contemporary Kantian approaches, and rights theory. What these approaches have in common is a strong foundation in philosophical *moral theory*, which allows them to identify clear sets of rules and obligations. As Beauchamp and Childress point out:

> For all their differences, utilitarians and deontologists conceive of moral philosophy and the demands of morality similarly: Ethics begins with the question, "What morally ought we to do?" and then provides general rules of obligation as guides to action.[83]

Given the wide range of ethical concerns involved in the implementation of novel neurobiological approaches to psychosis, I argue that a strong commitment to a particular normative philosophical theory will not serve the purpose of answering my research questions. This by no means implies that normative claims fall outside the remit of the present research. Indeed, assessing the impact of recent advances in medical technology requires that we investigate whether we *ought to* support, or reject, the introduction of these technologies into mental health care. However, I argue that an integrated and interdisciplinary approach built at the interface of several areas of ethics scholarship can better situate my claims and arguments. This is mainly for two reasons.

First, the purpose of the present research is to develop a framework that can support the ethical introduction of medical technology in mental health, by assessing the issues at stake as well as respecting the dignity, autonomy, and vulnerability of the actors involved. It is outside the remit of my research to provide

[83] Beauchamp, Tom L. and Childress, James F., *Principles of Biomedical Ethics* [7th edition] (New York: Oxford University Press, 2013), 375.

a Kantian, utilitarian, or human rights account of the ethics of novel neurobiological approaches to psychosis.

Second, let us follow the idea that ethics begins with the question, 'what morally ought we to do?' In order to answer this question we must know what we *can* do and refer to some kind of moral theory in order to figure out the 'ought to' part of the question. However, we must first figure out who is the 'we' that is implied in the question. In the context of this research, the 'we' cannot be assumed to include any rational human being. We *ought to* recognise that the 'we', in this research, includes patients, clinical researchers, mental health professionals, carers, and even policy makers and regulatory agencies. Each of these actors will respond to a different set of values. They will be characterised by a certain degree of agency and vulnerability, and will therefore be subject to different moral obligations. As much as I recognise the value of philosophical argumentation for the development of moral theory in bioethics, a straightforward ascription to a particular normative approach would be too artificial for the remit of this work.

I do not adopt a single normative approach in this thesis. Rather, I combine insights from different philosophical traditions in order to answer my research questions. I shall now sketch out the theoretical foundations of the framework I intend to propose. These include insights from the ELSI debate, an empirical ethics investigation of relevant stakeholders' perspectives, theoretical insights from vulnerability theory and care ethics, the regulation of clinical research, and mental health law.

1.4.1 From ELSI to integration

The ELSI approach was originally conceived at the end of the 1980s by James Watson as a theoretical tool to assess the implications arising from the expansion of genomic science into biomedicine and society. Despite being sometimes criticised for its (alleged) lack of critical oversight on the evolution of genomic science, it has since developed as a theoretical approach that facilitates

interdisciplinary interaction and policy development.[84] The identification of specific ELSI in the conduct of clinical research, clinical care, and public health applications is being expanded from its traditional focus on genomics to cognitive and clinical neurosciences. In the present work, I use the ELSI approach to identify the ethical, legal, and social concerns arising from the implementation of genomic and neuroscientific approaches to psychosis. I do not claim or believe that the ELSI approach can, on its own, exhaust the richness of ethical and legal reflections on recent advances in medical technology. Nonetheless, I believe that it represents an important tool for defining the boundaries of my inquiry, as well as for identifying potential legal and policy implications.

In Article one I explore the idea that, in assessing the moral implications of the convergence of neuroscience and genomics in the context of psychosis, we should move from the identification of different ELSI towards the *integration* of different ethical perspectives. I argue that ethicists should join efforts to address the moral implications of biomedical innovation in mental health. Further, in Article one I argue that the concept of *vulnerability* is a useful philosophical tool to achieve such theoretical integration. As I do not consider it appropriate to ground my framework in a particular normative approach, I shall now briefly explain what I intend with the idea of an integrated ethical framework.

First, an ethical framework that can help us to oversee the translation of neuroscience and genomics into mental health must *integrate* insights from several areas of ethics. Situated at the interface of clinical research and psychiatric care, such a framework must include findings from neuroethics, the ethics of psychiatric genomics, psychiatric ethics, the regulation of clinical research, and mental health law. This task might be accomplished by reflecting on the philosophical foundations of the ELSI approach, and through an (empirical) exploration of the values at stake. Second, this framework must *translate* relevant findings from different areas of bioethics into the mental health context. Borrowing the idea of translational ethics from Alan Cribb,[85] I argue that we must be aware of the social

[84] See for instance Kaye, Jane et al., 'ELSI 2.0 for Genomics and Society', *Science* 336 (6082) (2012): 673-674.
[85] Cribb, Alan, 'Translational ethics? The theory-practice gap in medical ethics', *Journal of Medical Ethics* 36 (4) (2010): 207-210.

dynamics that characterise the provision of mental health care in a given jurisdiction—in my case England and Wales. Particularly, this ethical framework must take into account the vulnerability of psychiatric patients, the peculiar clinician-patient relationship found in psychiatry, and the impact on patients' families and carers. Third, as the implementation of neurobiological approaches to psychosis has been to date mainly confined to clinical research, this ethical framework must *proactively* seek to identify ethical concerns that may derive from future clinical translation. This will be pivotal to ensure the ethical translation of research findings into clinical care as well as to support future policy developments.

1.4.2 An empirical ethics investigation

Considering the variety of social actors involved in the implementation of neurobiological approaches to psychosis, I argue that an empirical exploration of relevant stakeholders' perspectives is essential to identify their needs and to assess the values at stake. In doing so, I position the present research in the domain of *empirical bioethics* or, more precisely, empirical ethics in psychiatry.[86]

Over the past decades, the growing interest in empirical investigation in bioethics has been welcomed by a number of scholars as an empirical turn in bioethical inquiry.[87] However, the debate as to what role empirical data should have in informing normative reasoning has been fierce.[88] While most of bioethics scholarship remains anchored to a purely theoretical perspective,[89] empirical bioethicists have been apprehensive in justifying how a degree of openness towards quantitative and qualitative methods of social research can enrich the normative discourse, by shedding light on the values and perspectives hold by those very social actors who are the subject of bioethical investigation. It is not possible to provide a comprehensive account of such methodological debate in this introduction.

[86] See Widdershoven, Guy et al. (eds.), *Empirical Ethics in Psychiatry* (Oxford: Oxford University Press, 2008).
[87] See Borry, Schotsmans, and Dierickx, *op. cit.*; Kon, Alexander A., 'The Role of Empirical Research in Bioethics', *The American Journal of Bioethics* 9 (6-7) (2009): 59-65.
[88] See for instance Hurst, Samia, 'What 'empirical turn in bioethics'?', *Bioethics* 24 (8) (2010): 439-444.
[89] See Wangmo, Tenzin et al., 'An update on the "empirical turn" in bioethics: analysis of empirical research in nine bioethics journals', *BMC Medical Ethics* 19 (1) (2018): 6.

However, it is important that I briefly justify why, and how, the present thesis includes findings from an empirical ethics study.

The extent to which opponents of the empirical approach to bioethics have tried to demonstrate its epistemological unsoundness ranges from methodological concerns to a complete refusal. Professor John Harris is probably an exponent of the latter approach. As he wrote while discussing the implications of the so-called 'naturalistic fallacy':

> [M]uch contemporary bioethics and indeed even more contemporary policy making on ethics, seems to be committing a clearer and more vulgar fallacy, this we might call the "Empiricalistic Fallacy". […] Of course facts are fascinating and some facts are even essential, but gathering them is not the business of ethics. Empirical research of any sort is not ethical research. It might be essential to ethics, it may be the result of ethics, but ethics it ain't.[90]

While counter-arguing against the allegations of is/ought and naturalistic fallacy usually moved to empirical bioethics, John McMillan and Tony Hope note that these arguments do not count if we admit that empirical medical ethics cannot consist *only* of empirical work.[91] Empirical data gathered through qualitative or quantitative work must be contextualised against a theoretical framework, if we are to call it empirical *ethics*. In other words, I would argue, empirical research in bioethics is exactly what the name suggests: empirical research *in* bioethics. Qualitative research in ethics, for instance, aims to shed light on social actors' moral views and conceptualisations, which in the case of the present research is essential to enrich our theoretical framework and to make sense of the issues and values at stake.[92]

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[90] Harris, John, 'Putting Empirical Studies in Their Place', in Søren Holm and Monique F. Jonas (eds.), *Engaging the World: The Use of Empirical Research in Bioethics and the Regulation of Biotechnology* (Amsterdam: IOS Press, 2004), 18-27, 18-19.

[91] See McMillan, John and Hope, Tony, 'The possibility of empirical psychiatric ethics', in Guy Widdershoven et al. (eds.), *Empirical Ethics in Psychiatry* (Oxford: Oxford University Press, 2008), 9-22, 14.

[92] An invaluable account of the application of qualitative research methods in the context of medical ethics is provided by Holm, Søren, *Ethical problems in clinical practice. The ethical reasoning of health care professionals* (Manchester: Manchester University Press, 1997).

Here, I do not provide a defence of empirical ethics from the allegations of naturalistic fallacy or of breaching Hume's Law—deriving normative statements (ought) from descriptive ones (is).[93] This would require more than a short paragraph in this introduction. In order to substantiate my claims, I argue that one may take the last sentence in the previous quote by Harris: qualitative research findings are 'essential to ethics'. This provided they are acquired with a sound methodology and interpreted within an appropriate theoretical framework.

One example of this line of reasoning is provided by the ethical issue of *stigma* attached to mental disorders. If we asked the question, 'is social stigma attached to mental disorders morally good or ethically justifiable?', we would probably agree that the answer is 'no' without having to formulate any particular philosophical argument—at least in the context of bioethics, where many would agree that respect is owed to those who suffer from physical or mental illness. On the contrary, if we asked, 'what values and conceptualisations are at stake in the case of stigma attached to mental disorders?', or 'how do we tackle social stigma attached to mental disorders?', then we may want to investigate the views and experiences of the social actors involved. This might be a piece of sociological work, rather than philosophical work, but few would deny that such sociological work could enrich our *ethical* understanding of the phenomenon of social stigma attached to mental disorders. As Guy Widdershoven and Lieke van deer Scheer write:

> This process of listening requires openness. One should be prepared to see the perspective of the other as relevant to oneself. According to Gadamer, openness is the essence of hermeneutic understanding. One should be open to the claim to truth encountered in the perspective of the other.[94]

In this sense, the present work includes findings from a qualitative research study and is committed to the empirical turn *in* bioethics.

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[93] On the is-ought problem see the volume edited by Hudson, W. D. (ed.), *The Is-Ought Question: A Collection of Papers on the Central Problem in Moral Philosophy* (Macmillan and Co, 1969).
[94] Widdershoven, Guy and van der Scheer, Lieke, 'Theory and methodology of empirical ethics: a pragmatic hermeneutic perspective', in Guy Widdershoven et al. (eds.), *Empirical Ethics in Psychiatry* (Oxford: Oxford University Press, 2008), 23-35, 28.

Another pressing issue that characterises the debate over empirical ethics is *how*, and to what extent, scholars conducting empirical bioethics can draw normative conclusions from descriptive research—in other words, how the descriptive and the normative can be combined in empirical ethics.[95] I shall say more about how this issue has affected my research in Articles two and three as well as in the conclusions of this thesis. For now, I shall only say that the approach I use in this thesis owes some of its theoretical framing to what Raymond De Vries has called *descriptive ethics* and sociology *in* bioethics.[96] In the empirical investigation that I present in the coming pages, I conducted some sociological work to investigate how relevant actors think about, and respond to, important ethical issues in psychiatry. In Articles two and three, I do *not* draw strong normative conclusions from the data I gathered in my empirical work. Yet, the richness of these sociological findings allows me to make reflections, draw conclusions, and formulate recommendations that, as I shall argue, are relevant to the normative discourse. These findings, and the reflections I draw from them, are relevant to bioethics because they provide a qualitative-rich and empirically grounded context in which to frame normative analyses. They are relevant to bioethics, and to philosophical ethics, because they allow us to guide and (re)frame normative analysis.[97]

1.4.3 The ELSI-NAPS research study

Article two and Article three present findings from a qualitative research study I conducted as part of my empirical work. A detailed description of the methodology I used is provided in the articles. Additional materials such as interview and focus group guides and coding materials are provided in appendix. Here I describe the theoretical design and practical arrangements of the study, which constitutes the bulk part of my empirical ethics investigation.

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[95] See Davies, Rachel, Ives, Jonathan, and Dunn, Michael, 'A systematic review of empirical bioethics methodologies', *BMC Medical Ethics* 16 (2015): 15.
[96] De Vries, Raymond, 'How Can We Help? From "Sociology in" to "Sociology of" Bioethics', *The Journal of Law, Medicine & Ethics* 32 (2) (2004): 279-292.
[97] Buchbinder, Mara and De Vries, Raymond, 'The Ought and is of Conscience: The Value of Empirical Bioethics for Reframing Normative Analysis', *AJOB Empirical Bioethics* 11 (1) (2020): 27-29.

I entitled the study ELSI-NAPS—Ethical, Legal and Social Issues in Novel Neurobiological Approaches to Psychosis and Schizophrenia: A Qualitative Study. The aim of ELSI-NAPS was to answer research questions two and three that I outline in section 1.3 above. With ELSI-NAPS I wished to address the ELSI arising from the translation of neuroscience and genomics into clinical research and clinical care of psychotic disorders by investigating the perspectives of some relevant social actors.

ELSI-NAPS involved three study groups:

- Group A: researchers in psychiatry, psychology, or mental health employed in NHS facilities or in a university in England.
- Group B: mental health professionals employed in NHS mental health services. To account for variation of professional background, participants in group B included:
    - Mental health nurses
    - Social workers
    - Clinical psychologists
    - Psychiatrists
- Group C: carers or legal guardians of a psychiatric patient or service user suffering from a psychotic disorder or schizophrenia.

I used two qualitative research tools:

1. I conducted individual semi-structured interviews with researchers in group A and mental health professionals in group B in order to investigate their personal views through open questions, prompting, and probing. Interviews lasted for approximately one hour. They were audio recorded, transcribed verbatim, and analysed as described in Article two. In Article two I compare findings in group A and group B.
2. I conducted focus groups with carers in group C in order to investigate their conceptualisations as well as shared social norms through open questions,

discussion, and participant interaction. Each focus group included four to six carers. Focus groups lasted for approximately one and a half hour. They were audio-recorded, transcribed verbatim, and analysed as described in Article three.

The decision to adopt two different tools was based on the nature of the empirical investigation. I decided to conduct individual semi-structured interviews in the case of groups B and C because I wished to investigate the *personal* views of professionals in mental health—researchers and clinicians—and therefore individual interviews seemed the most appropriate research tool. At the same time, not only carers' conceptualisations but also shared social norms were under investigation in the case of group C. Therefore, focus groups appeared the most appropriate research tool to answer my research question in the second case.

The process of gaining research ethics approval included four steps:

1. Obtaining sponsorship and insurance by the University of Manchester via the university research governance, ethics and integrity office.
2. Undergoing NHS ethics review.
3. Obtaining approval from the Health Research Authority (HRA).
4. Receiving confirmation of capacity and capability to host the research from the Research and Innovation (R&I) office of the NHS Trust where part of participant recruitment was to take place, which included being granted a letter of access in order to access NHS premises to conduct the research.

I started designing ELSI-NAPS in the fall of 2016. I was granted sponsorship and insurance by the University of Manchester in April 2017. At the end of April 2017, I applied for NHS research ethics review. On 8 June 2017, I attended a meeting with North West—Greater Manchester South Research Ethics Committee. After requesting some minor amendments, the NHS REC granted ELSI-NAPS favourable ethical opinion on 12 July 2017 (reference number 17/NW/0315). The HRA also granted its approval to ELSI-NAPS on 12 July 2017. As I had decided to conduct part of recruitment in Greater Manchester Mental Health NHS Foundation

Trust (GMMH),[98] I then submitted my documentation to the Trust. I received confirmation of capacity and capability as well as my letter of access to the Trust from GMMH on 29 August 2017. ELSI-NAPS was registered on the publicly accessible database Research Registry, registration number researchregistry4255.

As I describe in more detail in Articles two and three, participant recruitment took place across different sites and locations and with different recruitment strategies. Between November 2017 and March 2018, I recruited and interviewed 14 researchers who worked in GMMH or in a university in England. Between February and August 2018, I recruited and interviewed 14 mental health professionals who worked in different roles across GMMH. Between May 2018 and January 2019, I recruited 15 carers by placing study posters in physical noticeboards across GMMH and by visiting charities and mental health carers groups across Greater Manchester to present my study. In this period, I conducted three focus groups with 4 to 6 carers each. In total, 43 participants were recruited for ELSI-NAPS. The end-of-study date was set on the day the last participant was to be recruited. This occurred on 5 January 2019.

I used a grounded theory approach to conduct ELSI-NAPS. Grounded theory is an epistemological and methodological approach developed within the social sciences.[99] Since its foundation, grounded theory has been widely used to design qualitative research in medicine and health-related contexts with the aim of exploring subjective conceptualisations of ethical issues.[100] Grounded theory approaches data collection and data analysis in an *iterative* process, in which hypotheses are not strictly derived from pre-existing theories and then tested through data collection and analysis, nor are theories solely developed from data analysis after data collection has been completed. Rather, grounded theory advocates for a constant and virtuous interaction between data collection and analysis to allow empirically grounded theory building. Grounded theory relies on

[98] Greater Manchester Mental Health NHS Foundation Trust provides a number of inpatient and outpatient mental health services in the Greater Manchester area, see https://www.gmmh.nhs.uk// last accessed 7 May 2020.
[99] See Corbin, Juliet and Strauss, Anselm, *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory* [IV edition] (London: SAGE Publication, 2015).
[100] See for instance Glaser, Barney G. and Strauss, Anselm L., *Awareness of Dying* (London and New York: Routledge, 2017/1965).

abductive reasoning: while hypotheses can drive and inform data collection, interpretations and theories are constructed through the iterative process of data collection and analysis.

In the case of ELSI-NAPS, using grounded theory allowed me to explore sensitive ELSI highlighted in the ethics debate while remaining receptive to novel theoretical insights that emerged from the discussion with study participants. The flexibility allowed by grounded theory was essential to gather unexpected insights from the iterative process of data collection and analysis. Outcomes of the ELSI-NAPS study were measured qualitatively using grounded theory analytic methods. Data analysis started prior to data collection being completed, though interview and focus group guides remained the same during the course of the study to allow for consistency in the questions asked and themes explored. Qualitative data collected from interviews and focus groups were thematically analysed following a stepped coding process in order to extract and compare relevant themes. I present detailed descriptions of the data analysis process in the "methods" sections of Article two and Article three.

1.4.4 Vulnerability theory and care ethics

When I outlined the theoretical foundations of my approach, I declared that a strong ascription to a particular normative theory would not help me to answer my research questions. However, the very nature of those questions points to some important philosophical underpinnings of my research. These are *vulnerability theory* and *care ethics*. The conceptual framework I adopt is grounded in the recognition of the moral status of care as central to the philosophical foundations of bioethics. More specifically, the philosophical approach I adopt rests on the idea that caring practices—a caring attitude can characterise not only the provision of care but also the conduct of research—are marked by the recognition of people's vulnerability and by the attempt to respect their dignity by recognising their needs, their values, and their embeddedness in a network of social relationships. As Beauchamp and Childress note, "[w]e need not reject principles of obligation in favour of the virtues

of caring, and we can conceive moral judgment as involving moral skills beyond those of specifying and balancing general principles."[101]

First, vulnerability theory plays an important role in my attempt to provide a blueprint for the integration of different lines of ethical inquiry. I do this in Article one. In this article, I discuss different philosophical notions of vulnerability. The notion of *universal* vulnerability has been explored by scholars working in feminist and care ethics. According to Martha Fineman, vulnerability is a—if not *the*—defining feature of the human condition, grounded in the fact that humans are embodied beings and thus they are intrinsically exposed to the possibility of being harmed.[102] At the same time, *population-based* accounts of vulnerability have historically shaped research ethics by identifying groups of individuals who are at greater risk of harm.[103] In Article one I argue that a nuanced understanding of the philosophical notion of vulnerability can help us to achieve the ethical integration needed to address technological convergence in psychiatry. In doing so, I borrow Florencia Luna's notion of *layers* of vulnerability, which is interestingly positioned within this debate.[104]

I must make a clarification. In discussing the regulation of clinical research in Article four, I sometimes use the notion of vulnerable populations. This may appear to contrast with the notion of vulnerability I develop in Article one, which rests on the idea of *layers of vulnerability* as factors that increase someone's likelihood of being harmed. I can explain why. In Article four, I analyse how regulatory instruments in England and Wales might shape the use of machine learning in clinical research. Regulations lay out legal requirements for research that depend on the individuals recruited: competent adults, minors, and adults who lack capacity. Research regulation displays an account of vulnerability based on group membership (minors/adults) and functional characteristics (mental capacity). Because I wish to discuss how this regulatory environment shapes clinical research,

[101] Beauchamp and Childress, *op. cit.*, 37.
[102] Fineman, Martha Albertson, 'The Vulnerable Subject: Anchoring Equality in the Human Condition', *Yale Journal of Law and Feminism* 20 (1) (2008): 1-23.
[103] See Bracken-Roche, Dearbhail et al., 'The concept of 'vulnerability' in research ethics: an in-depth analysis of policies and guidelines', *Health Research Policy and Systems* 15 (1) (2017): 8.
[104] Luna, Florencia, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *International Journal of Feminist Approaches to Bioethics* 2 (1) (2009): 121-139.

I am bound to reflect on vulnerable groups. Yet, my theoretical approach is the same in both articles. As in Article one, in Article four I investigate how the use of machine learning might introduce additional risks of harm in relation to individual (and contextual) factors, such as age and mental capacity. I shall say more about the notion of vulnerability in the conclusions of the thesis.

Second, vulnerability theory is connected to care ethics. Care can be thought of as a *response* to humans' vulnerability, which questions the way in which we frame our bioethical arguments.[105] The relevance of care ethics for my approach emerges primarily in Article three, where I contend that only by referring to an ethics of care can we appreciate the epistemic value of my empirical findings. As I argue in the article, carers' perspectives reveal a *different* outlook on the ethics of technological innovation in psychiatry; they reveal a narratively rich and epistemically valuable outlook on the issue of harms and benefits and on the moral challenges of technological convergence. By referring to the work of Joan Tronto, I argue that those who take on a caring role can reveal such a valuable moral outlook because their primary concern is the practical everyday needs of the person they care for; because "[w]hat is definitive about care […] seems to be a perspective of taking the other's needs as the starting point of what must be done."[106] Further, care ethics is relevant to my work because it highlights—as my empirical investigation also does—that carers' demands are not only ethical but also *political*, as they require a substantial restructuring of our societies.[107]

1.4.5 Regulatory oversight and psychosis prediction

In this section, I describe in more detail the *legal approach* I take in the articles and especially in Article four. Scientific discovery and technological development do not happen in a legal vacuum. Because they are social activities, they are shaped by the socio-legal environment in which they take place. In this thesis I investigate

[105] See for instance Gastmans, Chris, 'Dignity-enhancing nursing care: a foundational ethical framework', *Nursing Ethics* 20 (2) (2013): 142-149.
[106] Tronto, Joan C., *Moral Boundaries. A Political Argument for an Ethic of Care* (New York and London: Routledge, 1993), 105.
[107] See Held, Virginia, *The Ethics of Care: Personal, Political, and Global* (New York: Oxford University Press, 2006).

how the *regulatory landscape* in England and Wales can—and possibly should—shape the implementation of neuroscientific and genomic approaches to psychotic disorders. I achieve this by interrogating the sources of law that apply to the regulation of clinical research, data protection, and mental health care in this jurisdiction.

The main object of my research are the ethical and legal issues that arise from neurobiological—that is, from the convergence of neuroscientific and genomic—approaches to psychosis. One of the most important avenues for the clinical translation of neurobiological findings is the field of clinical prediction. One of the historical reasons, if not the most important reason, why clinical prediction is among the most promising avenues for the clinical translation of neurobiological findings is the rise of Artificial Intelligence (AI) and machine-learning methods in psychiatry.[108] I say 'historical' reasons because the rise of AI in medicine is a phenomenon that has characterised the last five to ten years with remarkable rapidity.[109] As noted by Jacob Turner, AI systems can be classified into *general* AI and *narrow* AI.[110] General AI is the "ability to achieve an unlimited range of goals, and even to set new goals independently" in a way that resembles human intelligence.[111] Conversely, narrow AI systems can only achieve the limited set of tasks they are designed to perform. Machine learning techniques are a subset of narrow AI whereby software is trained to classify data, develop algorithms automatically from the data, and make outcome predictions. The use of machine learning for psychosis prediction and the legal issues thereof are the object of my investigation in Article four.

In Article four I address the question: what legal challenges arise from the use of machine learning for psychosis prediction? Given my focus on the regulatory landscape of England and Wales, this general question becomes the narrower question: how do we *regulate* the use of machine learning for psychosis prediction

[108] See Shatte, Hutchinson, and Teague, *op. cit.*
[109] On the response of the bioethics community to the sudden rise of AI in medicine see the interesting perspective offered by Schuklenk, Udo, 'On the ethics of AI ethics', *Bioethics* 34 (2) (2020): 146-147.
[110] See Turner, Jacob, *Robot Rules. Regulating Artificial Intelligence* (Palgrave Macmillan, 2018), 6.
[111] Ibid.

in the jurisdiction of England and Wales? In answering this question, I look at several regulatory instruments available in this jurisdiction: statutes, applicable UK and EU regulations, and relevant case law from the Courts of England and Wales and from the European Court of Human Rights (ECtHR). As I specify above where I identify the sources of the law relevant to my work, these regulatory instruments pertain to two legal domains: (1) the regulation of clinical research and data protection and (2) mental health law. The reason why I focus my analysis on these two areas of law is that machine-learning applications for psychosis prediction are currently being developed at the interface of clinical research and mental health care.

In conducting my legal analysis in Article four, I focus on the issue of *risk*. Risk and prediction are inherently related from a clinical and a legal perspective. First, the notion of psychosis risk and the attempt to identify those who are at risk of psychosis have played an important role in the development of machine learning applications for psychosis prediction.[112] Second, at least since the Declaration of Helsinki, the balance between potential benefits and potential harms, or risks, to research participants has been central to the evaluation of clinical research.[113] International and domestic regulatory instruments define the principles according to which a certain balance between risks and benefits may be acceptable—and thus, lawful— for different research populations. Third, and most importantly, the issue of risk is central to mental health legislation in England and Wales.[114] In England and Wales, a person suffering from a mental disorder may be detained in hospital for assessment under section 2 or for treatment under section 3 of the Mental Health Act if, inter alia, this is "necessary for the health or safety of the patient or for the protection of other persons".[115] The Code of Practice to the Act specifies that the factors to consider in relation to the health or safety of the patient include *risk of harm* to self or others, broadly defined.[116] Further, risk assessment is particularly

[112] See Thompson and Broome (eds.), *op. cit.*
[113] See for instance Article 16 of the Declaration, "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects."
[114] See Glover-Thomas, Nicola, 'The age of risk: risk perception and determination following the Mental Health Act 2007', *Medical Law Review* 19 (4) (2011): 581-605.
[115] Mental Health Act 1983, Part II, section 3(2)(c).
[116] Department of Health, *Mental Health Act 1983: Code of Practice*, *op. cit.*, 114-115.

relevant for community treatment orders after a period of detention under the Act.[117] Risk assessment plays a significant role in the use of mental health legislation in England and Wales. These three notions of *risk*—psychosis risk, risks of research participation, and risk of harm under mental health law—are conceptually different and serve different purposes in legal theory. In Article four, I investigate how these different notions of risk (might) shape the regulation of machine learning for psychosis prediction.

Lastly, in conducting my analysis I refer to principles established by relevant case law. First, in the landmark case of *Winterwerp v. The Netherlands* the ECtHR established that objective medical expertise is needed to determine whether a person is of 'unsound mind' and to demonstrate the nature and degree of a mental disorder, in order for a deprivation of liberty to be lawful.[118] This principle is important as it prompts us to think what role clinical prediction might play in civil detention and in the deprivation of liberty of the mentally disordered. With regard to the risk of self-harm resulting from a mental disorder, the case of *Savage v. South Essex Partnership NHS Foundation Trust* established that there is an operational duty to protect the right to life of a detained patient under Article 2(1) of the ECHR, where a hospital knows, or ought to know, of a real and immediate risk to the life of the patient.[119] In *Rabone v. Pennine Care NHS Foundation Trust*, the UK Supreme Court held that this duty may be owed also to informal patients.[120] With regard to harm to others that could result from a mental disorder, in the case of *Osman v. United Kingdom*, the ECtHR established that public authorities must know of a real and immediate risk to the life of a person by a third party in order to enforce preventive measures.[121] In my analysis, I investigate how these legal

[117] Mental Health Act 1983, section 17B(2).
[118] (A/33) (1979-80) 2 EHRR 387, at para 39, "The very nature of what has to be established before the competent national authority – that is, a true mental disorder – calls for objective medical expertise. Further, the mental disorder must be of a kind or degree warranting compulsory confinement."
[119] [2008] UKHL 74, [2009] 1 AC 681; see also [2010] EWHC 865 (QB) in relation to damages awarded.
[120] [2012] UKSC 2, [2012] 2 AC 72. See also Allen, Neil, 'The right to life in a suicidal state', *International Journal of Law and Psychiatry* 36 (5-6) (2013): 350-357. Note that, in the language used in mental health legislation in England and Wales, an 'informal' patient is a patient who has voluntarily agreed to being admitted into hospital for assessment or treatment. An informal patient is thus *not* being held in hospital under the Mental Health Act 1983.
[121] (2000) 29 EHRR 245, at para 116.

principles on self-harm and harm to others might shape how machine-learning applications are used—and regulated—for clinical prediction in psychiatry.

1.5 Summary of the articles

The main body of the thesis is composed of four articles. Each of the articles addresses one of the four research questions I presented above in section 1.3. Here I briefly summarise the content of the articles.

Article one is philosophical. It draws from the ELSI debate on neuroscience and genomics to sketch out a theoretical approach that might help us to address the moral challenges of biomedical innovation in the context of psychosis. In this article, I ask the question 'should ethicists join efforts to tackle the ethical and legal issues that arise from novel neurobiological approaches to psychosis?' I argue that they should, and that ethics scholarship should proceed *beyond* the identification of a number of ELSI. I contend that we ought to respond to technological convergence in psychiatry by developing an *integrated* and patient-centred ethics approach. We should integrate insights from different areas of ethics, translate findings from bioethics into the mental health context, and proactively try to anticipate future ethico-legal concern that might arise in clinical translation. Then, I argue that this integrated approach should be focused on the assessment of individual vulnerabilities. I contend that the notion of *vulnerability* is an essential philosophical tool that can help us to achieve such theoretical integration. This is so, I argue, because potential harms to individuals who (might) suffer from psychosis can be conceptualised as stemming from different sources—or layers—of vulnerability. I borrow the notion of *layers* of vulnerability from Florencia Luna to describe how people who experience psychosis may be rendered vulnerable by individual and contextual factors. My argument is that this understanding of vulnerability might help us to integrate different lines of ethical inquiry to ensure that those who experience psychosis can benefit from, and not be harmed by technological convergence in psychiatry.

Article two presents findings from the ELSI-NAPS study. The article compares findings from interviews I conducted with 14 researchers in mental health (group A) and 14 mental health professionals (group B). It presents their views on the moral challenges of accessing neurobiological information—that is, information on genomic and brain correlates of psychosis, or information around risk status and illness susceptibility—in the context of psychosis. The two groups provided similar accounts of perceived moral challenges. Two main messages emerge from the findings. First, participants argued that the moral challenges that arise from accessing neurobiological information in the context of psychosis reach far beyond traditional research ethics and clinical ethics concerns. Second, neurobiological information was seen as a powerful tool in the narrative process through which individuals who (might) suffer from psychosis define their identity and establish personal and clinical goals. Overall, researchers and mental health professionals suggested that *acquiring* neurobiological information, even though morally relevant, might not be ethically problematic. On the other hand, how neurobiological information is communicated and used in research and in clinical care—in one word, how information is *delivered* to research participants and care recipients—poses substantive moral challenges. In the article I argue that appropriate ethical guidance, if not moral expertise, is needed to ensure that accessing neurobiological information may positively affect the development of individual self-narratives and the personal identity of those who experience psychosis.

Article three also presents findings from the ELSI-NAPS study. It presents results from the focus groups I conducted with 15 carers of a person suffering from psychosis. I investigated how carers conceptualise the ethical issues arising from novel neurobiological approaches to psychosis. The main message that emerges is one of *ambivalence*. To describe such ambivalence I report findings along three emotional axes: anger, hopes, and fears. These emotional axes summarise carers' ambivalent response to biomedical innovation in psychiatry. First, carers strongly demanded novel research and effective interventions that might support them in fulfilling their caring role and help their cared-for to live a flourishing life. Carers

hoped that technological innovation might be beneficial in meeting the needs of their cared-for. At the same time, carers feared that technological innovation might exacerbate common ethical issues in psychiatry and, eventually, produce more harms than benefits. They suggested that which way it goes will depend on whether their cared-fors' needs are appropriately assessed and met. In the article, I argue that carers provide a different outlook on the ethics of biomedical innovation in psychiatry, and that their narratives are an essential source of knowledge for bioethics. Further, I argue that carers' outlook on ethical issues can be properly understood only within an ethics of care, which recognises the moral salience of care as both practice and value.

Article four is legal. It draws from the fact that one of the most important avenues for the use of neurobiological findings in psychiatry is the field of machine-learning-based clinical prediction. In the article, I address the issue of how to regulate the use of machine learning for psychosis prediction with reference to the jurisdiction of England and Wales. The article has two objectives. First, I clarify which areas of English law are relevant to regulate the use of machine learning in *clinical research* on psychosis prediction. I argue that two areas of regulation are of particular relevance: protection of research participants and data protection. In exploring these two domains, I contend that the lawful implementation of machine learning will depend upon the legal requirements regarding the balance between harms and benefits of the research. These legal requirements vary depending on two factors: (1) additional risks introduced by the use of machine learning for data analysis and outcome prediction, and (2) the individuals who take part in the research, with reference to their age and mental capacity. Second, I investigate how the introduction of machine learning might affect the practice of *risk assessment* under English mental health law. I explore the notion of psychosis risk and that of risk of harm. I contend that reaffirming the distinction between these two notions is paramount to legal theory. I then discuss the impact that machine learning could have on coercion under mental health law. My argument is that, even though reducing diagnostic uncertainty in psychiatric assessment could benefit the mentally ill, it remains to be ascertained whether the use of machine learning might

benefit those who suffer from psychosis. I argue that the latter issue will rest on two factors: (1) which type of risk we are assessing, whether psychosis risk or risk of harm, and (2) what we are trying to predict, whether this is a psychosis transition, a psychotic relapse, self-harm and suicidality, or harm to others.

2. ARTICLE ONE | Psychosis, vulnerability, and the moral significance of biomedical innovation in psychiatry. Why ethicists should join efforts

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Summary

This article contributes to answering my thesis research question in three ways. First, along with the thesis introduction, it surveys the ethics literature on technological innovation in neuroscientific and genomic approaches to psychosis and their current convergence. It provides an overview on the question, "What ethical issues arise from the convergence of new technologies in tackling psychosis?" Second, this article answers the question, "How should bioethicists address the ethical issues that arise from technological convergence in the context of psychosis?" It argues that integrated bioethics might be a good solution. Ethicists should respond to technological convergence by developing an integrated and patient-centred approach. This implies recognising the value of ELSI research for

the identification of ethical, legal, and social issues while promoting increased collaboration across different sub-disciplines. In this sense, the article argues that ethicists should join efforts to tackle technological convergence in psychiatry. Third, this article argues that the philosophical notion of ‘vulnerability’ is an essential conceptual tool to achieve the ethical integration needed to tackle technological convergence. A nuanced understanding of vulnerability can provide some common ground for bioethicists to join efforts. The article presents a notion of ‘layers of vulnerability’ that can help us to identify individual and contextual factors that may increase someone’s likelihood of being harmed or wrong.

2.1 Abstract

The study of the neuroscience and genomics of mental illness are increasingly intertwined. This is mostly due to the translation of medical technologies into psychiatry and to technological convergence. This article focuses on psychosis. I argue that the convergence of neuroscience and genomics in the context of psychosis is morally problematic, and that ethics scholarship should go beyond the identification of a number of ethical, legal, and social issues. My argument is composed of two strands. First, I argue that we should respond to technological convergence by developing an integrated, patient-centred approach focused on the assessment of individual vulnerabilities. Responding to technological convergence requires that we (i) integrate insights from several areas of ethics, (ii) translate bioethical principles into the mental health context, and (iii) proactively try to anticipate future ethical concerns. Second, I argue that a nuanced understanding of the concept of vulnerability might help us to accomplish this task. I borrow Florencia Luna's notion of 'layers of vulnerability' to show how potential harms or wrongs to individuals who experience psychosis can be conceptualised as stemming from different sources, or layers, of vulnerability. I argue that a layered notion of vulnerability might serve as a common ground to achieve the ethical integration needed to ensure that biomedical innovation can truly benefit, and not harm, individuals who suffer from psychosis.

2.2 Introduction

Bioethics and mental health often had a difficult or at least uneasy relationship.[1] While bioethics has evolved into an interdisciplinary discourse around the ethical implications of technological innovation in biomedicine, mental health ethics has largely been dominated by issues of capacity, coercion, and involuntary hospitalisation of the mentally ill.[2] In this article I argue that the relationship between bioethics and mental health should, to some extent, be revised. An epistemological shift in the way we understand this relationship is required by the historical occurrences which have brought some of the hardest strands of biomedicine—neuroscience and genomics—to play a crucial role in the efforts to unveil the nature of mental illness and to find ways to prevent it, and cure it.

This article focuses on *psychosis*. The past few decades have seen a rapid increase in the use of neuroscience and genomics to investigate psychosis and susceptibility to psychotic disorders. On the one hand, neuroimaging studies are shedding light on the cognitive and neurobiological correlates of psychosis.[3] On the other hand, large cohort Genome-Wide Association Studies (GWAS) are playing an important role in the investigation of the genomic basis of psychosis, while whole genome sequencing is increasingly used to investigate susceptibility to psychotic illness.[4] More importantly, the study of the neuroscience and genomics of psychosis are increasingly *intertwined*. This is to a large extent due to technological convergence,[5] which I describe in this article as research convergence and data convergence. Along with potential clinical benefits, the translation of biomedical innovation into mental health gives rise to a number of ethical concerns which ought to be systematically addressed.

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[1] Holm, Søren, 'Bioethics and mental health — An uneasy relationship', *Ethics, Medicine and Public Health* 10 (2019): 1-7.
[2] Sadler, Van Staden, and Fulford (eds.), *op. cit.*
[3] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[4] Schizophrenia Working Group of the Psychiatric Genomics Consortium, *op. cit.*
[5] Floridi, Luciano, *The Fourth Revolution. How the Infosphere Is Reshaping Human Reality* (Oxford: Oxford University Press, 2014); Eyre, Harris A. et al., 'Convergence Science Arrives: How Does It Relate to Psychiatry?', *Academic Psychiatry: the Journal of the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry* 41 (1) (2017): 91-99.

My argument is composed of two strands. First, I argue that the current translation of biomedical innovation in the context of psychosis requires ethicists to join efforts in order to identify (and respond to) the moral challenges of technological convergence in psychiatry. In other words, I argue that technological convergence in psychiatry is morally problematic—or at least morally significant—and that we should respond to technological convergence with something we might call *ethical convergence*. I suggest that, although extremely important, the sole identification of a number of ethical, legal, and social issues may *not* be sufficient to ensure that we fulfil our duty to promote clinical benefits and minimise potential harms in technology translation. In the case of psychosis, I argue that we should respond to technological convergence by developing an integrated, patient-centred approach focused on the assessment of individual vulnerabilities. In order to do that, I suggest that we (i) integrate insights from several areas of ethics, (ii) translate findings from different areas of bioethics into the mental health context, and (iii) proactively try to anticipate ethical concerns that could derive from future clinical translation.

Second, I argue that the concept of vulnerability might be a useful philosophical tool to accomplish this task. The concept of vulnerability has a long history in research and care ethics and is currently undergoing a thorough theoretical redefinition.[6] Here, I borrow Florencia Luna's metaphor of *layers* of vulnerability to describe how the individual assessment of different sources (or degrees) of vulnerability might serve as a common ground for the identification of ethical issues in technological convergence.[7] I argue that we can conceptualise potential harms or wrongs to individuals who suffer from psychosis as stemming from different layers of vulnerability. I suggest that a nuanced understanding of vulnerability as it is currently emerging in research and care ethics might help us to

[6] Rogers, Wendy, Mackenzie, Catriona, and Dodds, Susan, 'Why Bioethics Needs a Concept of Vulnerability', *International Journal of Feminist Approaches to Bioethics* 5 (2) (2012): 11-38; ten Have, Henk, 'Respect for Human Vulnerability: The Emergence of a New Principle in Bioethics', *Journal of Bioethical Inquiry* 12 (3) (2015): 395-408.

[7] Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*; Luna, Florencia, 'Identifying and evaluating layers of vulnerability - a way forward', *Developing World Bioethics* 19 (2) (2019): 86-95.

achieve the ethical converge, or integration, which is needed to deliver practical solutions to ethical dilemmas in the context of psychosis.

2.3 Psychosis: biomedical innovation and technological convergence

Psychosis is not a discrete diagnostic category. It is an abnormal state of the mind, a set of symptoms characterised by a progressive detachment from reality. Mental disorders which are primarily characterised by psychotic symptoms, such as schizophrenia, are defined as psychotic disorders. Those who suffer from psychosis experience hallucinations, delusions, disorganised thinking and speech, and negative symptoms such as diminished emotional expression and social withdrawal.[8] Illness aetiology involves at the same time biological, psychological, and social factors.[9] While critiques of the biomedical model of mental illness continue to characterise the scientific debate, novel tools offered by neuroscience and genomics hold promise to unveil the neurobiology of psychosis.

Clinical research on the neurobiology of psychosis has been performed for decades.[10] The novelty of this approach does not lie in the attempt to unveil the neurobiological substrates of psychosis. Rather, the novelty lies in the development of new and more powerful medical technologies through which this attempt is carried out. More specifically, there are two aspects of novelty in recent neurobiological approaches to psychosis: the use of technology originally developed in biomedicine, particularly neuroimaging and next-generation sequencing, and the phenomenon of technological *convergence*. In turn, technological convergence can be described as (i) research convergence or convergence of different research approaches—in this case neuroscience and genomics, as exemplified by the Neuroscience in Psychiatry Network[11] or the UK

[8] American Psychiatric Association, *op. cit.*
[9] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[10] Ross et al., *op. cit.*; Read and Dillon (eds.), *op. cit.*
[11] Kiddle, Beatrix et al., 'Cohort Profile: The NSPN 2400 Cohort: a developmental sample supporting the Wellcome Trust NeuroScience in Psychiatry Network', *International Journal of Epidemiology* 47 (1) (2018): 18-19g.

Biobank project[12]—and (ii) data convergence or convergence of different data sources. Data convergence is evident in recent efforts to translate neurobiological findings into diagnostic tools that use machine learning to enhance diagnosis and prediction of psychosis.[13]

Let us explain this further. The neurosciences and genomics of psychosis constitute two distinct domains of investigation. Ethics usually targets one of the two, be it the use of neuroimaging in the context of mental illness[14] or the application of genomic science to psychiatry.[15] However, the two domains are inherently intertwined. Genomic science aims to unfold the molecular processes that govern hereditary patterns leading to neurophysiological and functional abnormalities—correlating with psychopathology—which in turn are the object of clinical neurosciences.

Amid recent developments, the decreasing cost of neuroimaging techniques has rekindled the interest in the neurosciences of psychosis. Magnetic Resonance Imaging (MRI) is used to investigate brain volume and structure in schizophrenia, the most replicated findings being decreased intracranial and total brain volume, along with alterations in grey matter structures.[16] Conversely, functional MRI (fMRI) is used to investigate regional brain activity as this reflects disrupted cognitive processes. In addition, molecular imaging techniques such as Positron Emission Tomography (PET), Single Photon Emission Tomography (SPET), and Magnetic Resonance Spectroscopy (MRS) are used to investigate neurotransmitter dysfunction and drug-receptor interaction.[17] Thanks to the use of these technologies, abnormal dopaminergic mechanisms have been confirmed to play a central role in psychosis, leading to the proposal of the 'dopamine hypothesis of schizophrenia–version III'.[18] The second development that is essential to mention is the introduction of Next-Generation Sequencing (NGS) into psychiatric genomics. This has resulted in the implementation of GWAS on psychosis and

[12] Elliott, Lloyd T. et al., 'Genome-wide association studies of brain imaging phenotypes in UK Biobank', *Nature* 562 (7726) (2018): 210-216.
[13] Shatte, Hutchinson, and Teague, *op. cit.*; Young, Kempton, and McGuire, *op. cit.*
[14] Bluhm et al., *op. cit.*
[15] Nuffield Council on Bioethics, *op. cit.*
[16] Haijma et al., *op. cit.*
[17] McGuire et al., *op. cit.*
[18] Howes and Kapur, *op. cit.*

schizophrenia. The most interesting findings are the identification of 108 schizophrenia-associated loci contributing to the risk of developing the disorder, along with insights from convergent functional genomics.[19] As research efforts made possible by the use of NGS progress, new discoveries will likely link our understanding of the genomic variations involved in susceptibility to psychosis with the neurobiological processes associated with illness progression. A clear example of this dynamic is the recent discovery that increased expression of the C4A gene is associated with an increase in *synaptic pruning*, which has been welcomed as a turning point in our understanding of the biology of schizophrenia.[20]

The convergence of neuroscience and genomics is also evident in the efforts to translate neurobiological findings into clinical care. Integrating genetic, cognitive, and multimodal neuroimaging data could support the classification of clinical populations and may help to identify individuals at high-risk of psychosis.[21] The search for markers of psychosis progression has the potential to support diagnosis and benefit treatment options. Possible markers of psychosis progression include, for instance, neuroanatomical markers in high-risk populations and neuro-functional markers in the psychosis prodrome.[22] Particularly promising are the attempts to develop tools for psychosis prediction. Recently, Koutsouleris et al. were able to correctly predict transition outcomes in high-risk individuals in 80% of cases using structural MRI data.[23] Even more exciting for many researchers is the developing field of psychosis prediction by integration of several data sets via machine learning and narrow artificial intelligence.[24]

[19] Schizophrenia Working Group of the Psychiatric Genomics Consortium, *op. cit.*; Ayalew et al., *op. cit.*
[20] Dhindsa and Goldstein, *op. cit.*
[21] Pettersson-Yeo, W. et al., 'Using genetic, cognitive and multi-modal neuroimaging data to identify ultra-high-risk and first-episode psychosis at the individual level', *Psychological Medicine* 43 (12) (2013): 2547-2562.
[22] Koutsouleris et al., *op. cit.*; Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[23] Koutsouleris et al., *op. cit.*
[24] Gifford et al., *op. cit.*; Shatte, Hutchinson, and Teague, *op. cit.*

2.4 Technological convergence and ethical, legal, and social issues

A case study[25]

Tom is seventeen years old. He lives with his mother Anna and his father David. David works odd jobs. He has a history of mental health problems and has received a number of diagnosis over the course of the years. Tom has always done very well in school, he likes playing football and going to concerts. However, in the last year Tom has been quite distressed. During a visit with the family doctor, Tom confessed that he has started hearing voices. The doctor referred Tom to the early intervention for psychosis team at the local psychiatric unit. The early intervention team has assigned Tom a care coordinator and offered that Tom attend talking therapy sessions. Meanwhile, a clinical research team is conducting a study within the psychiatric unit. They approach Tom and his family and offer that Tom be included in the research. Over the next six months, Tom would have to attend hospital visits once a month for neuroimaging scans. A single blood draw would be performed during the first visit to allow for genetic analysis. In addition, Tom would be given a smartphone that collects behavioural data to monitor his mental health. A smartphone app would help Tom to cope with episodes of voice hearing and allow him to communicate with the research team.

Tom's story exemplifies the theoretical density which characterises technological convergence in mental health. What moral challenges can we identify in Tom's story?

Should medical technologies be translated into mental health care? The mere fact that biomedical innovation is being translated into mental health care represents *per se* a development worthy of ethical scrutiny, given the opposition that psychosocial approaches have traditionally expressed towards the biomedical model of mental illness and its history of involuntary hospital admissions and social

[25] This case study is largely based on a focusing exercise which I used during focus groups within the ELSI-NAPS research study, registration number: researchregistry4255, NHS REC reference: 17/NW/0315. The wording of the case study has been slightly modified from the original version in the focusing exercise.

control.[26] In other words, one may argue that medical technology should be translated into mental health care *only if* we accept the biomedical model of mental illness. The biomedical model is not universally recognised as valid, considering the complex spectrum of aetiological theories of mental illness. In this article I accept—for the sake of the argument— that the biopsychosocial model of mental illness is valid, and that therefore biomedical innovation has a legitimate role in tackling psychosis.

In recent years, several ethicists have started to identify a number of Ethical, Legal, and Social Issues (ELSI) that characterise the expansion of neuroscience and genomics into mental health. The development of neurobiological approaches to psychosis is situated at the *intersection* of several ethics domains. Referring to the ELSI literature might help us to shed light on the moral challenges that characterise our case study.

First, (neuro) ethicists have started to address the ELSI that arise from the use of neuroimaging in different clinical domains, including psychiatry. Racine and Illes have provided a useful platform for identifying the ethical challenges of advanced neuroimaging research.[27] In their comprehensive review, the authors list a number of areas of concern, including management of Incidental Findings (IFs), informed consent, privacy and confidentiality, impact on vulnerable populations, and stigma and discrimination. The links between neuro-essentialist thinking and stigma attached to mental illness play a central role in understanding the societal challenges related to the translation of neurobiology into psychiatry.[28] In addition, the use of neuroimaging for diagnosing a psychotic disorder could affect the sense of responsibility and agency of young individuals. Boyce has also noted how the introduction of neuroimaging in psychiatry could result in the excessive adoption of the medical model, potentially affecting clinician-patient relationships and increasing the risks of medicalisation and over-diagnosis.[29]

[26] Read, John, Mosher, Loren, and Bentall, Richard P., "Schizophrenia' is not an illness', in John Read and Jacqui Dillon (eds.), *Models of madness. Psychological, social and biological approaches to psychosis* [2nd edition] (London & New York: Routledge, 2013), 3-8.
[27] Racine and Illes, *op. cit.*
[28] Haslam, *op. cit.*
[29] Boyce, *op. cit.*

Second, psychiatric genetic research might exacerbate ethical concerns traditionally found in genomics. For instance, the question of which results should be communicated to participants is being widely debated given the difficulty of interpreting NGS results, and the potential impact of such information on participants' life choices. Lázaro-Muñoz et al. argue that additional guidance should be available for evaluating which results should be returned to participants in psychiatric genetic research.[30] This issue overlaps with the question of how to manage IFs in psychiatric genomics. In their review of the ethical issues at the intersection of psychiatric genomics and mental health treatment, Kong et al. also mention the connection between genetic essentialism and stigma as a major ethical concern.[31] In addition, as highlighted by Appelbaum and Benston, the potential development of psychiatric genetic testing renews a number of ethical concerns regarding the translation of psychiatric genomics into the wider domains of general and reproductive health.[32]

Third, important legal issues arise at the intersection of research and care. To mention some, the introduction of medical technologies in research on psychosis generates concerns about informed consent. How do researchers obtain informed consent from (young) individuals who suffer from psychosis? How should they? What about individuals who are defined as being at risk of psychosis, but have not (yet) suffered from a psychotic episode?[33] In this regard, how will the logic of risk in psychosis prediction interact with the practice of risk assessment and involuntary hospital admission under mental health legislation?[34] Further, GWAS in psychiatry as well as neuroimaging studies generate great amounts of health-related sensitive data. Data handling and sharing will be dependent upon data protection frameworks in different jurisdictions.

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[30] Lazaro-Munoz, G. et al., 'Improved ethical guidance for the return of results from psychiatric genomics research', *Molecular Psychiatry* 23 (1) (2018): 15-23.
[31] Kong, Dunn, and Parker, *op. cit.*
[32] Appelbaum, Paul S. and Benston, Shawna, 'Anticipating the Ethical Challenges of Psychiatric Genetic Testing', *Current Psychiatry Reports* 19 (7) (2017): 39.
[33] Morris, Sarah E. and Heinssen, Robert K., 'Informed consent in the psychosis prodrome: ethical, procedural and cultural considerations', *Philosophy, Ethics, and Humanities in Medicine* 9 (1) (2014): 19.
[34] Corsico, Paolo, 'The risks of risk. Regulating the use of machine learning for psychosis prediction', *International Journal of Law and Psychiatry* 66 (2019): 101479.

In table 1, I try to list the most relevant ELSI that arise from the convergence of neuroscience and genomics in the context of psychosis. This list does not pretend to be exhaustive. I do not claim that the sole identification of a number of ELSI provides sufficient grounds to address them. Rather, as I explain later, I claim quite the opposite. In the list, I also attempt to identify the most relevant ethical concerns in our case study, Tom's story.

Table 1. ELSI that arise from the convergence of neuroscience and genomics in the context of psychosis.

	Neuroscience	**Neuroscience & Genomics**	**Genomics**
Research	Neuroimaging research governance	- Return of results - Management of Incidental Findings - Lack of immediate clinical utility - Challenges for REC / IRB review	- NGS research governance
Research & Care	- Neuro-essentialism - Potential applications in forensic psychiatry	- Informed consent - Impact on identity and agency - Privacy and confidentiality - Data management and sharing	- Genetic essentialism
Clinical / Psychiatric Care	- Impact on treatment options & compliance	- Stigma & self-stigmatisation - Impact on clinician-patient relationship - Risk assessment and communication - Risk of over-diagnosis - Resource allocation - Impact on families and carers	- Regulation of genetic testing and screening - Potential development of Direct To Consumer psychiatric genetic testing - Risk of genetic discrimination

Tom's story and the above ELSI review demonstrate that technological convergence in the context of psychosis is situated at the *intersection* of several ethics domains. The same could be said of mental health conditions other than psychosis. Therefore, I believe that we need an epistemological shift in the way we understand the relationships between bioethics and mental health. I do *not* claim

that the ELSI approach is not well suited to identify the moral challenges of biomedical innovation in psychiatry. Instead, I argue that the phenomenon of technological convergence may require ethicists to go *beyond* the identification of ELSI in different domains, and to consider joining efforts in what we might call *ethical convergence*, in order to address the moral significance of biomedical innovation in psychiatry. I clarify my argument in the following pages.

2.5 Should ethicists join efforts to address biomedical innovation in the context of psychosis?

As exemplified by Tom's story, an intricate knot of ELSI characterises the convergence of neuroscience and genomics in the context of psychosis. This knot is situated at the intersection of several ethics domains. How do we untie it?

My argument is meta-ethical in nature. To be more precise, my argument is *not* meta-ethical in the sense of being developed within the scope and aims of (analytic) meta-ethics.[35] I am not attempting to establish the nature of moral claims using the conceptual tools developed within the meta-ethics tradition. Instead, I use the word 'meta-ethical' to indicate that my argument is *not only* an ethical argument, as it is primarily located at the epistemological level rather than at the normative level. In this sense, my argument is 'meta' ethical as it goes beyond the identification of moral principles to discuss the epistemological relationships among different branches of ethical inquiry. The argument goes as follows:

1. Clinicians and researchers have (and, to a certain extent, share) a moral obligation to promote clinical benefits and minimise potential harms in technology translation, notwithstanding the different moral obligations related to their specific professional role.[36]

[35] Sayre-McCord, Geoff, 'Metaethics', *The Stanford Encyclopedia of Philosophy (Summer 2014 edition)*, updated 26 January 2012, https://plato.stanford.edu/archives/sum2014/entries/metaethics/, last accessed 18 December 2019.

[36] Given the fact that I am discussing the use of *medical* technology in mental health, this moral obligation is grounded in the principles of beneficence and non-maleficence, which apply—even though in different ways—to clinicians and researchers alike, see Beauchamp and Childress, *op. cit.*

2. Potential harms can be conceptualised as stemming from the different sources (or *layers*) of vulnerability, which characterise different individuals who suffer from psychosis.
3. The ELSI approach is useful to identify layers of vulnerability and potential harms / wrongs. However, this may not be sufficient. We must integrate insights from different areas of ethics and ELSI research, in order to ensure that different individuals receive the appropriate protection to which they are entitled by virtue of their (degree of) vulnerability.

Point (1) of my argument is grounded in the principles of beneficence and non-maleficence. It serves as a major premise and, as a postulate, it also grounds the ELSI discourse on biomedical innovation in the context of psychosis. For these reasons, I do not think it is necessary to discuss it here. The concept of (layers of) vulnerability is then central to my analysis.[37] It is an essential philosophical tool that provides some common ground, a blueprint for the integration of different ethical perspectives. Placing the vulnerability of individuals who (may) suffer from psychosis at the core of our ethics discourse might help us to ensure that, in addressing each of the identified concerns, we can establish the appropriate level of protection to which each individual is entitled. I shall argue why I believe that the concept of vulnerability may still be useful in the next section of this article. Before I do that, I wish to justify point (3) of my argument by asking again, how do we untie the intricate knot of ELSI? Let us consider our options.

Option (a) is that we try to establish a new ethics sub discipline. For instance, Cheung has argued that we need a new ethics of psychiatry, which may help us to identify and address the ethical challenges posed by the development of translational neurosciences and by the use of neuro-technology in psychiatry.[38] Option (b) is that we keep identifying ELSI arising from neuroscience and genomics, and we then try to provide appropriate solutions in the specific case of psychosis. Lastly, option (c) is that we try to integrate insights from different ethics

[37] Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*
[38] Cheung, Erick H., 'A new ethics of psychiatry: neuroethics, neuroscience, and technology', *Journal of Psychiatric Practice* 15 (5) (2009): 391-401.

and ELSI sub disciplines in a patient-centred approach based on the assessment of individual vulnerabilities.

Option (a) sounds promising. However, it may not be currently viable for two reasons. First, we may disagree on whether we need a 'new ethics of psychiatry'. Even if we could reach a consensus on the matter, establishing a new discipline may prove more difficult than declaring the need for it, whereas some of the ELSI identified require a prompt response. In the ten years that have passed since Cheung formulated this proposal, neuroethics has developed as a fully independent discipline. However, albeit sometimes overlapping, neuroethics and psychiatric ethics still remain separate, given that the former mainly focuses on neuro-technology and brain conditions and the latter on mental illness.[39] Second, even within a 'new ethics of psychiatry' we would still need to provide appropriate solutions in the specific case of psychosis. We would also still need to integrate findings from other ethics sub disciplines, as it would be unrealistic to think that a new discipline could provide novel solutions to all issues addressed by other sub disciplines.

I believe that option (b) best describes current scholarly efforts. Within option (b), we may effectively address the ELSI identified in the case of psychosis, as the growing literature demonstrates. However, option (b) comes with two risks. First, we risk that when addressing each ELSI we may not consider the *interaction* among different ELSI. More specifically, as shown in the above review, the ELSI discourse tends to focus on *either* the neuroscience *or* the genomics of psychosis. By limiting our analysis to this approach, we risk losing the bigger picture and forgetting that we are talking about the same individuals, as exemplified in Tom's story, who must deal with issues of consent, stigma, and neuro and genetic essentialism, only to mention some. In turn, there is a risk that regulation may be driven by only one, or some, of the identified concerns. Second, by not considering the interactions between the ELSI discourse in neuroscience and genomics, we might not be able to provide sufficient grounds to establish whether a specific technology *ought to* be translated in clinical practice.

[39] Illes and Sahakian (eds.), *op. cit.*; Sadler, Van Staden, and Fulford (eds.), *op. cit.*

Option (c) implies that we integrate insights from different ethics sub disciplines in a patient-centred approach focused on the assessment of individual vulnerabilities. It requires that we reflect on what happens, or may happen, to individuals who suffer from psychosis. This would help us to assess not only the impact of neuroscience and genomics in the context of psychosis but also, and more importantly, their convergence and interaction. By adopting option (c) we are prompted to recognise two facts. First, the conduct of clinical research is grounded in the value of scientific knowledge. Yet, this has to be weighed against potential harms and wrongs to research participants. As I describe later in more details, potential harms and wrongs can be conceptualised as stemming from different (individual) layers of vulnerability. Second, the translation of medical technology in psychiatry is grounded in the principle of beneficence, as it aims to ameliorate prevention, diagnosis, and treatment for individuals who suffer from psychosis. However, non-maleficence mandates that people are not exposed to unnecessary risks and harms. In the case of (young) individuals who suffer from psychosis, establishing whether the risks of participating in clinical research are acceptable, or whether treatment options may be beneficial or not, will require that we consider *all* the ELSI involved, as well as their interactions.

For these reasons, I support option (c). At a practical level, I suggest that ethicists should 'join efforts' to meet the moral challenges posed by technological convergence in psychiatry, as the case of psychosis appears to demonstrate. At the epistemological level, I believe that we can further specify three *recommendations* which I think are embedded in this proposal.

First, as argued above, we should *integrate* insights from different areas of ethics and ELSI scholarship. While we progress in identifying ELSI arising from the translation of medical technology in psychiatry, adopting an integrated and patient-centred approach will ensure that the particular needs of (young) individuals who suffer from psychosis remain at the core of our ethics reflection. Second, we should *translate* findings from different areas of bioethics into the mental health context. It is of course important to acknowledge that mental health should receive the same level of attention and, proportionally, the same level of resources as physical health. However, in some respect, mental health is qualitatively different

from physical health. The impact of psychosis on people's sense of identity and the cultural understandings of mental illness ought to be taken into consideration.[40] Ethical recommendations drawn in the context of physical health—such as the ones formulated for brain imaging or genomics—must undergo appropriate translation when formulated in context of psychosis. Performing this translation requires that ethical recommendations take at least into account: (i) cultural perceptions of mental health conditions, including stigma; (ii) the peculiarity of caring practices and clinician-patient relationships in psychiatry; (iii) the impact of mental health legislation on regulatory environments. Appropriate translation of ethical recommendations is essential to ensure that they can be properly enacted by the relevant actors involved. Third, we should *proactively seek to anticipate* ethical concerns that may derive from technology translation into clinical care. Technological convergence in the context of psychosis has been, to date, primarily confined to clinical research. However, as I have argued above and as exemplified in our case study, clinical translation is already underway. While medical technologies move from research to care, it is essential that we try to anticipate imminent ethical, legal, and social challenges. The different degrees of vulnerability of psychiatric populations mandate a high level of awareness regarding future clinical developments. The idea of a proactive approach to the ethical evaluation of novel technologies—as opposed to a reactive approach in ethics— is already being discussed regarding neuro-engineering, assistive, and rehabilitation technologies.[41] Adopting a proactive approach will be important in order to promote the ethical translation of research findings into clinical care.

2.6 Why the concept of vulnerability may (still) be useful

Point (2) of my argument is that 'potential harms can be conceptualised as stemming from the different sources (or *layers*) of vulnerability which characterise

[40] Boydell, Katherine M. et al., 'A descriptive review of qualitative studies in first episode psychosis', *Early Intervention in Psychiatry* 4 (1) (2010): 7-24; Patel, Maya et al., 'Health beliefs and carer burden in first episode psychosis', *BMC Psychiatry* 14 (2014): 171.

[41] Ienca, Marcello et al., 'Proactive Ethical Design for Neuroengineering, Assistive and Rehabilitation Technologies: the Cybathlon Lesson', *Journal of NeuroEngineering and Rehabilitation* 14 (1) (2017): 115.

different individuals who suffer from psychosis'. The assessment of individual vulnerabilities is central to my analysis. I believe that the concept of vulnerability may still be a useful philosophical tool to guide the ethical integration I describe above. Identifying ethical issues in technological convergence means—to a certain extent—identifying clinical and personal benefits which must be weighed against potential harms or wrongs. How does the concept of vulnerability help us to accomplish this task? In what sense are individuals who (may) suffer from psychosis vulnerable?

Vulnerability is a concept with a long history that spans moral philosophy, research ethics, care ethics, and feminist ethics.[42] It is beyond the scope of this article to provide a comprehensive account of vulnerability theory. Yet it is important to explain why this concept is useful to our analysis.

A common definition of vulnerability—staying close to the etymology of the term—is that being vulnerable means 'being open to the possibility of being wounded', or being at risk of harm.[43] On the one hand, universal accounts of vulnerability recognise that, as embodied beings, *all* humans can be wounded and thus all humans are intrinsically vulnerable. Care is often defined as a response to the intrinsic vulnerability that characterises all human beings.[44] Philosophical accounts such as the one proposed by Martha Fineman consider vulnerability a central feature of the human condition which should ground the political discourse around equality.[45] On the other hand, the notion of *vulnerable populations* has been used in research ethics to identify groups of people who deserve special protection because of their greater likelihood of being harmed.[46] This second, population-based account of vulnerability has historically led to the establishment of stronger safeguards for certain groups—among which are people who suffer from mental illness—but also to their unfair exclusion from research.[47]

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[42] Rogers, Mackenzie, and Dodds, *op. cit.*
[43] Hoffmaster, Barry C., 'What Does Vulnerability Mean?', *Hastings Center Report* 36 (2) (2006): 38-45; ten Have, *op. cit.*
[44] Gastmans, *op. cit.*
[45] Fineman, *op. cit.*
[46] See The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979).
[47] DuBois, James M., *Ethics in Mental Health Research. Principles, Guidance, and Cases* (New York: Oxford University Press, 2008).

The idea that those who suffer from mental illness are a vulnerable population is present, for instance, in the 2002 Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines for biomedical research or in the EU Clinical Trials Regulation 536/2014.[48] However, the population-based account of vulnerability has been heavily criticised. Levine et al. have highlighted its stereotyping nature and ineffectiveness in protecting individuals from harm.[49] Luna has argued that a labelling approach based on the idea of vulnerable populations fails to recognise the ways in which individuals are *rendered* vulnerable by social and relational factors.[50] More recently, Bracken-Roche at al. have criticised the population-based notion of vulnerability in the case of psychiatric research participants. They argue that such notion is based on stereotypes around the (lack of) decisional capacity of people who suffer from mental illness, which can lead to paternalism and stigmatisation.[51] At the same time, many authors—and among those Luna and Bracken-Roche—argue that the notion of vulnerability ought *not* to be discarded, but revised.

The notion of *layers* of vulnerability developed by Luna[52] can help us to understand how individuals who suffer from psychosis are vulnerable, and why this is relevant to the ethical evaluation of biomedical innovation in psychiatry. Individuals who suffer from psychosis are not vulnerable because they belong to the population of the mentally ill. They are not vulnerable *simply* because of their psychosis. Vulnerability is somehow distinct from diagnostic categories, also because (i) diagnostic categories are historical entities which evolve over time,[53] and (ii) with reference to the growing field of psychosis prediction, individuals who are *at risk* of psychosis may be recognised as vulnerable in the absence of a specific diagnosis. In this sense, individuals who may suffer from psychosis are not more

[48] Bracken-Roche et al., 'The concept of 'vulnerability' in research ethics: an in-depth analysis of policies and guidelines', *op. cit.*
[49] Levine, Carol et al., 'The limitations of "vulnerability" as a protection for human research participants', *The American Journal of Bioethics* 4 (3) (2004): 44-49.
[50] Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*
[51] Bracken-Roche, Dearbhail, Bell, Emily, and Racine, Eric, 'The "Vulnerability" of Psychiatric Research Participants: Why This Research Ethics Concept Needs to Be Revisited', *The Canadian Journal of Psychiatry* 61 (6) (2016): 335-339.
[52] Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*; Luna, 'Identifying and evaluating layers of vulnerability - a way forward', *op. cit.*
[53] Guloksuz, S. and van Os, J., 'The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum', *Psychological Medicine* 48 (2) (2018): 229-244.

vulnerable than all other human beings who are at risk of harm because of some form of illness. At the same time, in rejecting a population-based account of vulnerability we must recognise that individuals who experience psychosis may be *rendered* vulnerable by individual and contextual factors. These factors constitute what Luna calls 'layers' of vulnerability. Layers of vulnerability do not automatically characterise certain groups. Instead, an individual assessment of different sources, or layers, of vulnerability can serve as a common ground for the identification of ethical issues.

Let us focus on Tom's story. In what sense is Tom vulnerable? Broadly speaking, Tom is vulnerable because he is in a situation that could benefit him but also increase his likelihood of being harmed. How could Tom be harmed? First, we should consider *individual* factors as a first layer of vulnerability. We can recognise two important individual factors:

1. Tom's *capacity* to consent to research or treatment: Tom's decisional capacity is likely to be affected by his age—he is seventeen—and by his psychotic symptoms. It would be paternalistic to say that Tom lacks capacity only because of his age and mental illness. At the same time, it is important to assess Tom's decisional capacity *precisely* because his age and mental illness can affect his ability to appreciate what taking part in research might involve.
2. The fact that Tom is unwell and help-seeking: this fact can increase Tom's chances of being harmed where the duty of care might lose precedence over the duty to produce knowledge. It also establishes different moral obligations for clinicians and researchers.

Second, we should consider *contextual* factors as a second layer of vulnerability. In this sense Luna's layered account of vulnerability is relational.[54] We can recognise at least two important sets of contextual factors in Tom's story:

[54] Luna, 'Identifying and evaluating layers of vulnerability - a way forward', *op. cit.*

1. Family dynamics: not only could Tom's condition affect his family's relational dynamics. Accessing information on brain processes and genetic predisposition to psychosis could be perceived as either empowering or distressing by different family members.
2. The social context: the social and cultural context can impact on Tom's likelihood of being harmed and render him vulnerable. Those who suffer from psychosis are often subject to social stigma and discrimination.[55] In addition, in many jurisdictions people who suffer from mental illness may be subject to coercion and involuntary hospitalisation.[56] Whether this may benefit or harm them is debatable. Yet, it clearly limits the extent to which these individuals can exercise their autonomy.

This overview of different sources of vulnerability is not meant to be exhaustive. My argument here is only that a nuanced understanding of the ways in which Tom, and people in a situation similar to Tom's may be rendered vulnerable can help us to ensure that potential harms are minimised and potential benefits—or occasions to flourish—maximised. In this sense potential harms (or wrongs) to individuals who suffer from psychosis can be conceptualised as stemming from different layers of vulnerability. A layered account of vulnerability can serve as a common ground for the identification of ethical issues in technological convergence, and can be a useful philosophical tool to develop an integrated and patient-centred approach to technology translation.

Luna further rejects the idea of developing fixed *taxonomies* of vulnerability.[57] Other bioethicists such as Kenneth Kipnis insist on the importance of identifying taxonomies that may be useful to ethical inquiry.[58] I do not wish to enter this debate here. Yet, I wish to highlight three more reasons why a revised

[55] Yang et al., *op. cit.*
[56] de Stefano, Alessia and Ducci, Giuseppe, 'Involuntary Admission and Compulsory Treatment in Europe: An Overview', *International Journal of Mental Health* 37 (3) (2008): 10-21.
[57] Luna, 'Identifying and evaluating layers of vulnerability - a way forward', *op. cit.*
[58] Kipnis, Kenneth, 'Vulnerability in Research Subjects: A Bioethical Taxonomy', *Ethical and Policy Issues in Research Involving Human Participants. Volume II: Commissioned Papers* (Bethesda, Maryland: National Bioethics Advisory Commission, 2001), G1-G13.

notion of vulnerability might help us to integrate the ELSI discourse around the neuroscience and genomics of mental illness.

First, as argued by Henk ten Have, 'respect for human vulnerability' is increasingly recognised as an emerging bioethical principle which can ground normative analysis.[59] This fact points us to the necessity of rethinking our accounts of vulnerability, but also to the need *not to discard* the very notion of vulnerable individuals. Second, a nuanced and theoretically rich notion of vulnerability can be useful to both research and clinical ethics.[60] Such a notion can help us to address ethical issues at the intersection of research and care, and to identify potential harms and benefits arising from technological convergence in psychiatry. Lastly, a layered notion of vulnerability, as the one proposed by Luna, might help us to develop a relational and participatory account of vulnerability in psychiatry. Within a relational account of vulnerability we may recognise that vulnerability is not a feature of certain groups but a *relation* between individual and contextual factors, which may put some people at increased risk of harm. Further, if we wish to find out how Tom—or people in a situation similar to Tom's—are or may be rendered vulnerable, why not discuss this directly with them? A participatory account of vulnerability highlights that it might be a good strategy to involve directly individuals who experience psychosis in establishing *how* they are or may be rendered vulnerable.[61]

2.7 Conclusions

How could the proposed framework support bioethical inquiry? Let us consider a brief example. Psychosis prediction via machine learning could soon make its way into psychiatric care.[62] It will likely be achieved by integrating several data sets including neuroimaging, genomic, and behavioural data. First, in order to address the moral challenges of psychosis prediction via machine learning we must

[59] ten Have, *op. cit.*
[60] Hurst, Samia A., 'Vulnerability in research and health care; describing the elephant in the room?', *Bioethics* 22 (4) (2008): 191-202.
[61] Bracken-Roche, Bell, and Racine, *op. cit.*
[62] Corsico, 'The risks of risk. Regulating the use of machine learning for psychosis prediction', *op. cit.*

integrate insights from the (neuro) ethics of brain imaging, the ethics of psychiatric genomics, and consider issues of big data governance. This because we ought to ensure that vulnerable individuals are appropriately safeguarded, in research as in clinical care. Second, recommendations formulated in the context of physical health must be translated in the context of mental health to retain their operational validity. We must assess how machine learning will be regulated in different jurisdictions and how mental health legislation will shape regulatory environments. Lastly, it will be important to adopt a proactive approach, as machine learning is still not extensively used in mental health care. Anticipating the ethical challenges that psychosis prediction via machine learning could generate will help us to ensure that individuals receive the protection to which they are entitled by virtue of their (degree of) vulnerability.

Technological convergence is ubiquitous in biomedicine. In this article I have tried to show how, in the case of psychosis, technological convergence takes the form of an attempt to unveil the neurobiology of psychosis with tools offered by neuroscience and genomics. At the intersection of research and care, such attempt is directed towards the development of better ways of predicting, diagnosing, and treating psychotic illness. I have argued that technological convergence in psychiatry is morally problematic. It requires us to start rethinking the uneasy relationships between bioethics and mental health. I have proposed that we direct our attention to the vulnerability which characterises individuals who (may) suffer from mental illness. We should cross traditional boundaries among different areas of ethics and promote an integrated approach based on the assessment of individual and contextual sources—or layers—of vulnerability. In other words, I have argued that ethicists should join efforts to respond to the moral challenges of technological convergence in psychiatry. A revised and philosophically rich notion of vulnerability might help us to accomplish this task. Further, I recognise the centrality of patients and service users in assessing the ways in which they could be harmed or helped to flourish by technological convergence.

By doing so we might take a first step towards ensuring that those who suffer from mental illness receive the appropriate protection to which they are entitled. This may imply, for instance, that novel predictive tools are not translated into

psychiatry unless there is sufficient evidence for claiming some form of clinical utility. Or it may imply that specific informed consent procedures are put in place when recruiting asymptomatic individuals at risk of psychosis in clinical research involving neuroimaging or genomic procedures. In this article, I did not directly address any of these potential implications. Rather, I have supported the meta-ethical claim that bioethicists, neuroethicists, and legal scholars should join efforts in addressing these developments. Technological convergence requires us to rethink how those of us who suffer from mental illness are or may be rendered vulnerable, and how they can be helped to flourish. In this sense, psychosis is only one occurrence within the spectrum of mental health conditions. Yet, psychosis may provide us with an occasion to reflect on how to ensure that medical technology truly benefits those who experience mental ill health and are at increased risk of harm.

3. ARTICLE TWO | "It's all about delivery". Researchers and health professionals' views on the moral challenges of accessing neurobiological information in the context of psychosis

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Summary

This article contributes to answering my thesis research question by exploring the impact that technological convergence has on the moral worlds of two groups of social actors: researchers and health care professionals. The article is based on the assumption that investigating how social actors conceptualise moral challenges can help bioethicists to reframe normative analysis and to address the ethical issues of technological convergence. The theoretical justification of this assumption has been presented in the thesis introduction. The article presents findings from an empirical ethics qualitative study. The convergence of new technologies results in the increased availability of neurobiological information—that is, information around brain and genomic correlates of psychosis, or information around risk status and illness susceptibility—in research and in clinical care. This article investigates how researchers and health professionals conceptualise the moral challenges of

accessing neurobiological information in the context of psychosis. The qualitative investigation revealed that researchers and health care professionals perceive the acquisition of neurobiological information as not particularly problematic. Yet, they argue that substantial moral challenges arise from how neurobiological information is delivered—that is, communicated and used—in research and care. This because of the impact that information delivery can have on the *identity* of patients and services users. A nuanced understanding of the impact that technological convergence has on the availability of neurobiological information and appropriate ethical guidance on how such information should be delivered are needed to ensure that technological convergence may truly benefit, and not harm, people who suffer from psychosis.

3.1 Abstract

Background

The convergence of neuroscience, genomics, and data science holds promise to unveil the neurobiology of psychosis and to produce new ways of preventing, diagnosing, and treating psychotic illness. Yet, moral challenges arise in neurobiological research and in the clinical translation of research findings. This article investigates the views of relevant actors in mental health on the moral challenges of accessing neurobiological information in the context of psychosis.

Methods

Semi-structured individual interviews with two groups: researchers employed in the National Health Service (NHS) or a university in England (*n*=14), and mental health professionals employed in NHS mental health services (*n*=14). This article compares results in the two groups (total *n=28).*

Results

This article presents results around three areas: (i) research ethics as mostly unproblematic, (ii) psychosis, bio-information, and mental health care, and (iii) identity, relationships, and the future. Researchers and health professionals provided similar accounts of the moral challenges arising from the acquisition, communication, and use of bio-information in the context of psychosis. Acquiring neurobiological information was perceived as mostly unproblematic, provided ethical safeguards are put in place. Conversely, participants felt that substantive moral challenges arise from how neurobiological information is delivered— that is, communicated and used—in research as in clinical care. Neurobiological information was seen as a powerful tool in the process through which individuals define their identity and establish personal and clinical goals. The pervasiveness of this narrative tool may influence researchers and health professionals' perception of ethical principles and moral obligations.

Conclusions

This study suggests that the moral challenges that arise from accessing neurobiological information in the context of psychosis go beyond traditional research and clinical ethics concerns. Reflecting on how having access to neurobiological information can influence individual self-narratives will be vital to ensure the ethical translation of neuroscience and genomics into mental health.

Trial registration

The study did not involve a health care intervention on human participants. It was retrospectively registered on 11 July 2018, registration number: researchregistry4255.

3.2 Introduction

The convergence of clinical neurosciences, next-generation genomics, and data science is leading the way towards a deeper understanding of the neurobiology of mental illness.[1] Psychotic disorders are among the most debilitating forms of mental illness. Two strains of research are currently shedding light on the neurobiology of psychosis. First, over the past decades neuroimaging has allowed researchers to identify neuro-cognitive correlates of psychosis.[2] Second, the expansion of molecular genomics and next-generation sequencing is playing a pivotal role in unveiling the bases of inheritability of psychotic disorders as well as the molecular processes involved in disrupted neuro-cognitive development, which in turn leads to vulnerability to psychosis.[3] Several scholars further claim that the *convergence* of bio-information availability and data science has the potential to transform mental health care via public health approaches and artificial intelligence.[4]

Accessing neurobiological information in the context of psychosis generates several moral challenges. Not only must researchers deal with issues of mental capacity and research participants' vulnerability.[5] Other theoretical and practical problems arise. First, given the difficulty of translating neurobiological findings into clinical applications, it might appear more difficult to justify neurobiological research in the first place. Joseph goes as far as advocating for a moratorium on schizophrenia genetic research.[6] From the opposite viewpoint, Insel has highlighted the need to rethink the very concept of schizophrenia while affirming the relevance of neurobiology in redefining diagnostic categories.[7] Second, neuroimaging and genetic research on psychotic illness generate ethical dilemmas. How should we

[1] Bogdan, Ryan et al., 'Imaging Genetics and Genomics in Psychiatry: A Critical Review of Progress and Potential', *Biological Psychiatry* 82 (3) (2017): 165-175; Eyre et al., *op. cit.*
[2] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[3] Dhindsa and Goldstein, *op. cit.*; Sekar, Aswin et al., 'Schizophrenia risk from complex variation of complement component 4', *Nature* 530 (7589) (2016): 177-183; Gratten et al., *op. cit.*
[4] Insel, 'Translating scientific opportunity into public health impact: a strategic plan for research on mental illness', *op. cit.*; Young, Kempton, and McGuire, *op. cit.*; Shatte, Hutchinson, and Teague, *op. cit.*
[5] DuBois, *Ethics in Mental Health Research. Principles, Guidance, and Cases*, *op. cit.*
[6] Joseph, Jay, ''Schizophrenia and heredity'. Why the emperor (still) has no genes', in John Read and Jacqui Dillon (eds.), *Models of madness. Psychological, social and biological approaches to psychosis* [2nd edition] (London & New York: Routledge, 2013), 72-89.
[7] Insel, Thomas R., 'Rethinking schizophrenia', *Nature* 468 (7321) (2010): 187-193.

manage incidental findings in psychiatric neuroimaging research?[8] Is there a moral obligation to return the results of psychiatric genetic research to participants?[9] Third, it is unclear what impact having access to neurobiological information may have on the identity of mental health patients and how neuro-information could affect their family and social relationships.[10] Will having access to one's neuro-information be beneficial to the development of the self-narratives of those who experience psychosis? Will it be detrimental to their journey towards recovery?

This article does not tackle these issues with robust philosophical arguments. Nor does it support any strong normative claim. Rather, it provides a glimpse into the moral life of relevant actors in mental health. By 'moral life' I mean the ways in which different actors describe and frame the ethical challenges of their professional roles in the everyday practice of research and care. Historically, the convergence of neuroscience and genomics to tackle psychosis has been situated in an overly-polarised cultural milieu, which is very different from the one found in physical health. The fight between biological and psychosocial approaches to mental illness has been raging for decades and it is far from being resolved.[11] Within this fight, biological psychiatrists often see the implementation of neuroimaging and genomics as a mandatory step towards the development of effective treatments and public health agendas, while psychosocial scholars tend to reject such framings on ethical and political grounds.[12] Within this fight, the present article is an exercise of aetiological *neutrality*. It contends that by exploring the views of professionals with different backgrounds across the aetiological divide we might help to inform the ethical debate, at least by situating moral principles and obligations within the practical reasoning of the very individuals who should *enact* those principles and

[8] Racine and Illes, *op. cit.*; Wolf, *op. cit.*

[9] Lazaro-Munoz et al., *op. cit.*; Kostick, Kristin M. et al., 'Psychiatric genetics researchers' views on offering return of results to individual participants', *American Journal of Medical Genetics Part B Neuropsychiatic Genetics* 180 (8) (2019): 589-600.

[10] Postan, Emily, 'Defining Ourselves: Personal Bioinformation as a Tool of Narrative Self-Conception', *Journal of Bioethical Inquiry* 13 (1) (2016): 133-151.

[11] Bentall, *Madness Explained. Psychosis and Human Nature*, *op. cit*; Read, John, Haslam, Nick, and Magliano, Lorenza, 'Prejudice, stigma and 'schizophrenia'. The role of bio-genetic ideology', in John Read and Jacqui Dillon (eds.), *Models of madness. Psychological, social and biological approaches to psychosis* [2nd edition] (London & New York: Routledge, 2013), 157-177.

[12] Insel, 'Translating scientific opportunity into public health impact: a strategic plan for research on mental illness', *op. cit.*; Read, Mosher, and Bentall, *op. cit.*

fulfil those obligations.[13] Further, it builds upon the assumption that exploring such views may help bioethicists to redefine their arguments by considering real-world implications of principles and obligations.[14]

This article presents findings from interviews that I conducted with two groups: researchers in mental health and mental health professionals. I sought to investigate how these groups understand, and respond to, the moral challenges of accessing neurobiological information in the context of psychosis, as well as the moral challenges of using neuro-information in the clinical encounter. I investigated how researchers and health professionals conceptualise: (i) the moral challenges of conducting neurobiological research—that is, neuroimaging and genomic research—in the context of psychosis, and (ii) the moral challenges of using neurobiological information in clinical interventions for psychosis.

Two terminological clarifications are needed. First, throughout the article I use the expression 'in the context of psychosis' to refer to research conducted with individuals with an established diagnosis as well as research that investigates neurobiology in prodromal or (healthy?) at-risk individuals.[15] I recognise that these two populations have different ethical and legal profiles.[16] However, the focus of this article is on the moral challenges of accessing neurobiological information *related to* psychosis—that is, information around genomic and brain correlates of psychosis, or information around risk status and illness susceptibility— regardless of the actual diagnosis of research participants and care recipients. This tension was made explicit to participants in this study, and an indication of which populations the different interview questions refer to can be found in the interview guides. I also clarify this in the results. However, a certain degree of ambiguity is maintained. I believe that this ambiguity may signal the pervasiveness of the ethical ramifications of biomedical innovation in psychiatry. Second, in this article I use the word 'acquiring' neurobiological information only to describe actions performed by

[13] Holm, *Ethical problems in clinical practice. The ethical reasoning of health care professionals*, *op. cit.*; De Vries, *op. cit.*
[14] Solomon, Mildred Z., 'Realizing Bioethics' Goals in Practice: Ten Ways "Is" Can Help "Ought"', *Hastings Center Report* 35 (4) (2005): 40-47.
[15] Fusar-Poli et al., 'The psychosis high-risk state: A comprehensive state-of-the-art review', *op. cit.*
[16] Broome, Matthew, Fusar-Poli, Paolo, and Wuyts, Philippe, 'Conceptual and Ethical Issues in the Prodromal Phase of Psychosis', in K. W. M. Fulford et al. (eds.), *The Oxford Handbook of Philosophy and Psychiatry* (Oxford: Oxford University Press, 2013), 779-802.

researchers or health care professionals and not by patients or service users. I do not consider direct-to-consumer applications. Conversely, I use the words 'accessing' and 'using' neurobiological information to describe actions performed by professionals and patients / service users, who may access information in research and also use information in clinical care.

3.3 Methods

This article presents the first set of results of a larger research study entitled ELSI-NAPS: Ethical, Legal and Social Issues in Novel Neurobiological Approaches to Psychosis and Schizophrenia—A Qualitative Study. ELSI-NAPS also included focus groups with carers of a person suffering from psychosis. Focus group data are *not* discussed here.

3.3.1 Data collection

One-time, semi-structured individual interviews were held with participants in two groups: researchers (group A) and mental health professionals (group B). Inclusion criteria for participants in group A were: (i) being a researcher in clinical psychology, psychiatry, or clinical neurosciences, with a research interest in psychosis or schizophrenia, employed in a National Health Service (NHS) facility or in a university in England; (ii) good spoken English; (iii) having a PhD or a clinical doctorate. Inclusion criteria for participants in group B were: (i) being a mental health professional with at least one year of work experience with psychotic populations, employed in an NHS community mental health service or inpatient unit; (ii) good spoken English; (iii) having an undergraduate degree. To account for variation of professional background, participants in group B included mental health nurses, social workers, clinical psychologists, and psychiatrists.

I used *purposive* sampling to identify potential participants.[17] For group A, I identified researchers via websites of universities in England. For group B, I

[17] Bryman, Alan, *Social Research Methods* [IV edition] (New York: Oxford University Press, 2012); Battaglia, Michael P., 'Purposive Sample', in Paul J. Lavrakas (ed.), *Encyclopedia of Survey Research Methods* (Thousand Oaks: SAGE Publications, 2011), 645-647.

identified mental health professionals across community mental health services in Greater Manchester Mental Health NHS Foundation Trust. Potential participants were contacted via email and offered participation if they met inclusion criteria. All participants provided written informed consent and completed a demographic questionnaire prior to the interview. They received no incentive for their participation. Participants could have their travel expenses reimbursed if they wished so. Each interview lasted for approximately 45 minutes and took place either in the participant's office, in a private meeting room at the participant's workplace, or in a public meeting room.

I used two interview guides. The interview guides were designed to direct discussion towards participants' views as these related to their professional experience. Hence, the two guides focused on analogous ethical issues but diverged with regard to the context where ethical issues and moral dilemmas arise. For the researchers, the interview guide focused primarily on ethical issues arising in *clinical research* and then touched upon moral challenges in clinical practice. For the mental health professionals, the interview guide briefly referred to ethical issues in clinical research and then focused mostly on moral challenges in *clinical practice*. The interview guides are presented in Appendix A.

3.3.2 Data analysis

Data collection and data analysis were performed as an *iterative* process.[18] Data analysis began before data collection was completed. This allowed me to inform subsequent interviews. The interview guides remained the same during recruitment to ensure consistency of topics covered. Interviews were audio recorded and transcribed verbatim. Transcripts were anonymised and pseudonyms are used in this article. Transcripts were analysed in a stepped thematic analysis process.[19] After a first initial reading, codes were developed that captured the arguments articulated by participants. Codes (themes) were grouped in higher order categories and the categories were organised under different topics explored in the interviews.

[18] Corbin and Strauss, *op. cit.*
[19] Braun, Virginia and Clarke, Victoria, 'Using thematic analysis in psychology', *Qualitative Research in Psychology* 3 (2) (2006): 77-101.

Two distinct coding structures and coding manuals for the two groups were inductively developed from the transcripts. In a second phase, two other researchers independently reviewed the coding manuals against 5 of the 28 transcripts (3 transcripts for group A and 2 transcripts for group B) to ensure reliability. The coding manuals were revised by incorporating reviewers' comments, and consensus was reached. In a third phase, the transcripts were transferred to NVivo 11 software and the new coding structures and manuals were used to code all the transcripts. Some codes were eventually adjusted during this process. After all the transcripts had been coded I used the analysed data to compare results in the two groups and to write this article. The final thematic map which combines the two coding structures can be seen in Table 1. The final coding manuals are presented in Appendix B.

3.4 Results

14 researchers in group A and 14 mental health professionals in group B were recruited between November 2017 and July 2018 (total *n*=28). Participant demographics can be seen in Table 2. Most researchers described their research field as either clinical psychology (*n*=7) or psychiatry (*n*=5). The majority of them stated that they had received some ethics education in the form of Good Clinical Practice (GCP) training, while half of them stated that they had received further ethics training. Most mental health professionals worked as either mental health nurses (*n*=5) or social workers (*n*=3). Half of them stated to have received GCP training, and only four said that they had received further ethics training. Table 1 presents the combined *thematic map*. Themes are organised into sub-categories, which are then grouped into broader topics. Eight topics emerged from discussions with the researchers in group A: arguments for and against research, returning results, incidental findings, lack of clinical utility, essentialist thinking, impact, stigma and labelling, and clinical translation. Seven topics emerged from discussions with professionals in group B: arguments for and against research, essentialist thinking, impact, stigma and labelling, clinical translation, effects of novel diagnostic tools, and genetic testing.

Table 1. Thematic map: Normal font=researchers; *italics=health professionals*; **bold=both**

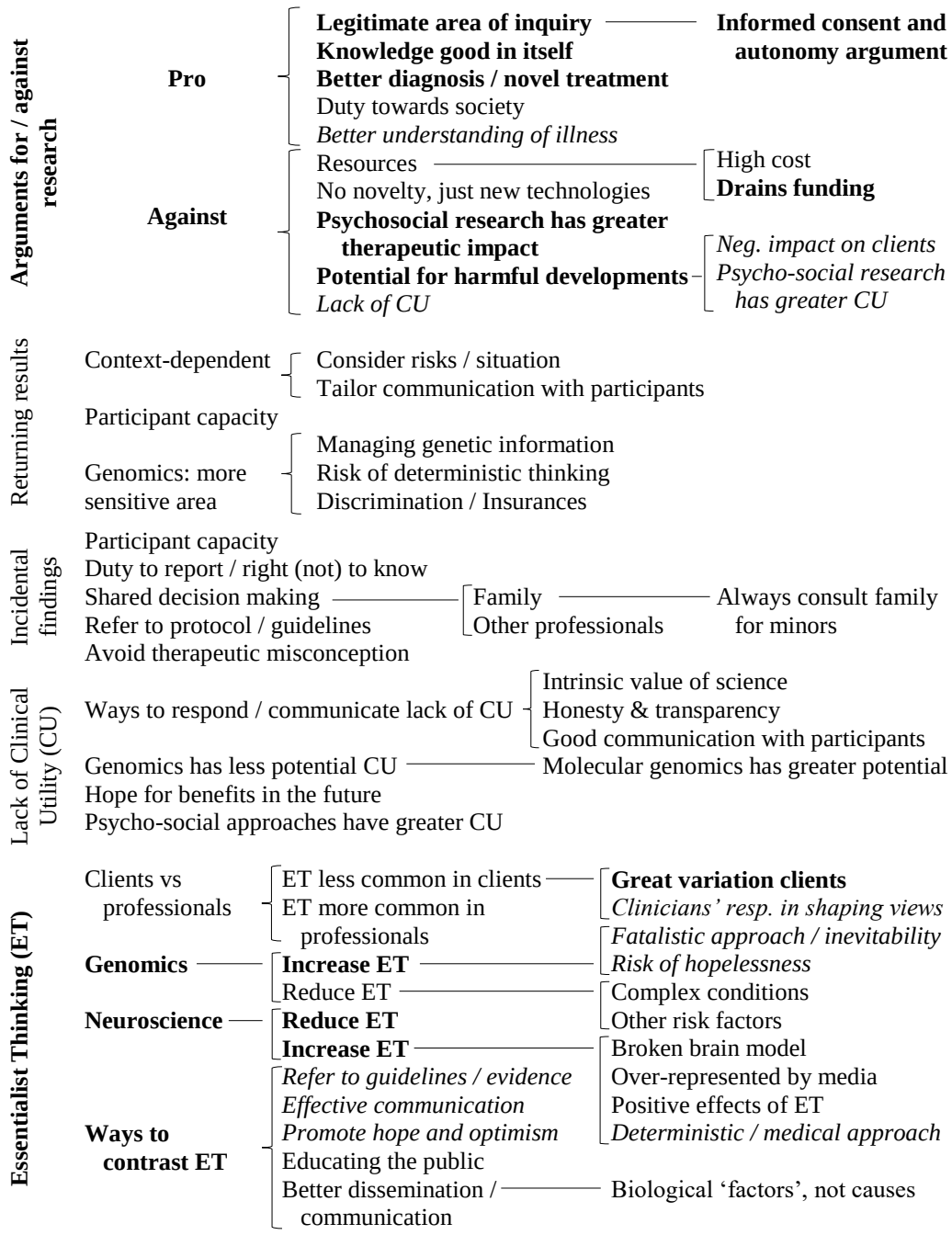

Table 1 (continued). Thematic map: Normal font=researchers; *italics=health professionals*; **bold=both**

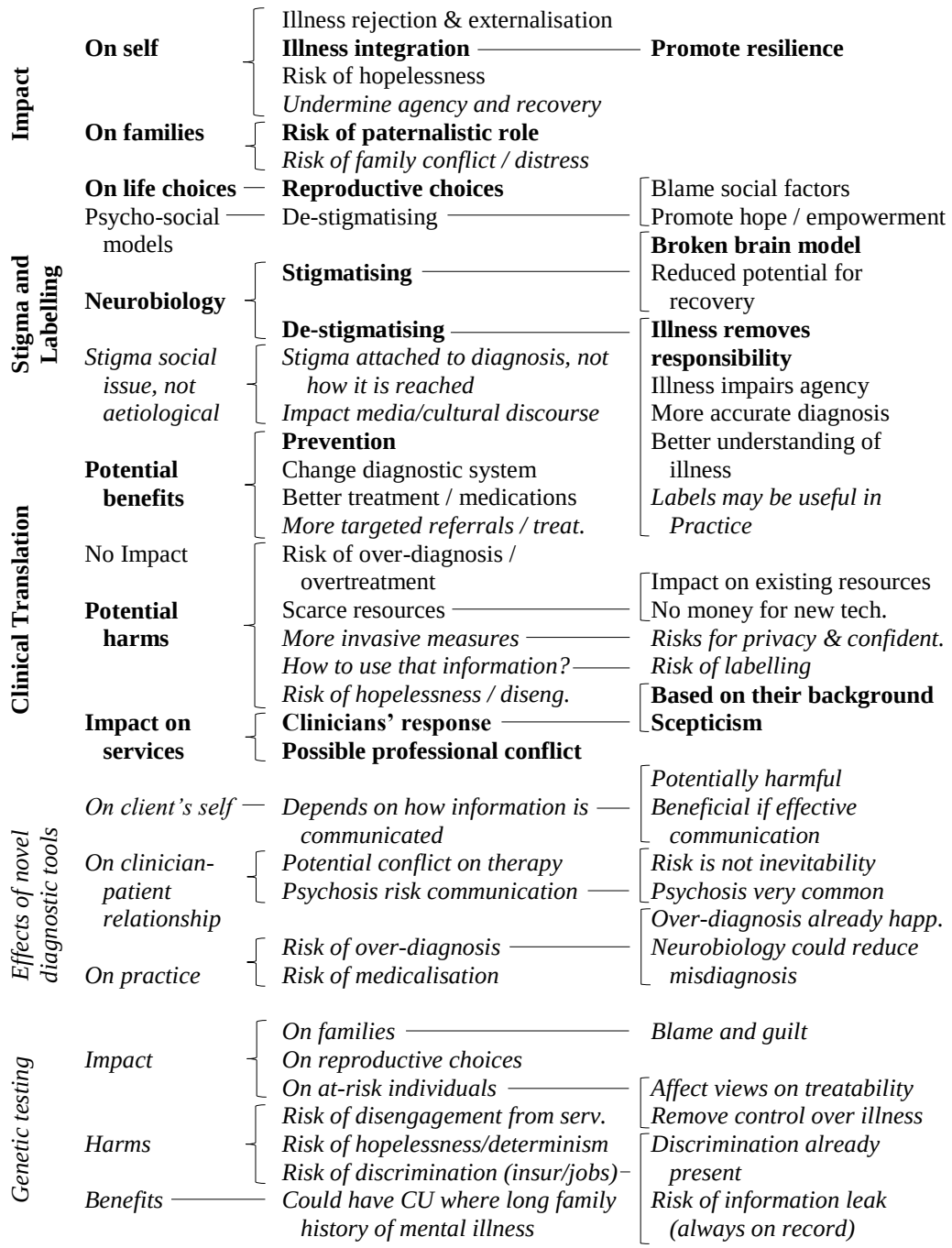

Table 2. Participant demographics; *GCP = Good Clinical Practice training

	Age	Gender		Education	Ethics training
			Main research field		
Researchers *n*=14	[33-74] Median=44 Mean=45.3	M=8 (57.2%) F=6 (42.8%)	Clinical Psychology=7 Psychiatry=5 Education=1 Psychosis=1	PhD=10 Clinical doctorate=3 Both=1	GCP=12 (85.7%) Other=7 (50%)
			Occupation		
Mental Health Professionals *n*=14	[37-64] Median=42 Mean=46.1	M=6 (42.8%) F=8 (57.2%)	Mental health nurse=5 Social worker=3 Psychiatrist=2 Psychotherapist = 1 Counsellor=1 Clinical psychologist=1 Care coordinator=1	Doctorate=2 Postgrad.=8 Undergrad.=3 Not disclosed=1	GCP=7 (50%) Other=4 (28.6%)

In this article I present results around three areas. These areas are drawn from the topics listed above whereby different topics are presented together—across the two groups of participants—because of their conceptual affinity. The section "research ethics as mostly unproblematic" presents results on: arguments for and against research in both groups, and returning results and incidental findings in group A. The section "psychosis, bio-information, and mental health care" presents results on: lack of clinical utility in group A, clinical translation in both groups, and effects of novel diagnostic tools in group B. Lastly, the section "identity, relationships, and the future" presents results on: essentialist thinking, stigma and labelling, and impact in both groups, and genetic testing in group B.

3.4.1 Research ethics as mostly unproblematic

Researchers and health professionals provided a number of arguments to justify conducting neurobiological research on psychosis. Despite the current lack of clinical applications, participants in both groups argued that neurobiology yields

the potential to improve the understanding of psychosis, redefine diagnostic categories, and produce better treatments. The neurobiology of psychosis was generally recognised as a legitimate area of scientific inquiry regardless of participants' professional background. Further, both researchers and professionals argued that individuals who suffer from a psychotic disorder should not be assumed to lack capacity to consent to research *only* because of their diagnosis. Individuals who are deemed to have capacity to take part in research should be treated as any other (healthy) individual with regard to providing informed consent. Two justifications were presented for this argument. The first justification focused on autonomy:

> Again I suppose I keep returning to a kind of Kantian framework for this, if the patients are happy to take part and we want to do it, well who's telling us we shouldn't be doing what we all want to do, you know, where's the big harm that nobody's decided to take on?
>
> Researcher, psychiatry

According to this argument it would be *paternalistic* to take decisions regarding participation in neurobiological research on behalf of capacitous patients or service users. The second justification focused on justice and non-discrimination. It would be unfair to exclude capacitous individuals from neurobiological research because of their mental illness:

> I would never make decisions on behalf of service users to say 'I really think this isn't good for you'. I would weigh up some of those decisions with them personally but I'm of the opinion that I like to give people all the opportunities that might be [avail]able for them, and for them to make their own minds up.
>
> Health professional, clinical psychologist

On the other hand, many participants highlighted the fact that neuroscience and genomics are 'costly' enterprises. Neurobiological research risks shifting useful

resources and draining funding away from psychosocial research which in turn—as some participants argued—has proved to have greater clinical utility. Some participants also stressed that research into the neurobiology of psychosis is not new and that the claimed novelty of neuroimaging and molecular genomics only lies in the use of more sophisticated technologies.

I asked researchers about returning results and disclosure of incidental findings. Researchers generally supported the idea that they have a *duty* to communicate aggregate results and that participants should, if they wish, be offered the opportunity to know the main findings. Interestingly, most researchers recognised that the same obligations apply to the disclosure of individual results, thus echoing recent debates which problematise the distinction of researchers' obligations with regard to returning genomic results.[20] Even though researchers recognised practical differences in returning aggregate or individual results, their main concern was not *whether* to disclose but *how* to disclose such information—with reference to communication strategies—and what *type* of information is disclosed, as they highlighted significant differences between neuroscience and genomics in this regard. Researchers stressed the importance of tailoring communication with participants to the capacity, age, and clinical status of the individual, and the duty not to expose participants to potential risks related to disclosure of aggregate / individual findings:

> I suppose if you're having some investigations, then you have a duty to give the results, don't you. So, I think that that's important. I suppose it depends what the message is and how you deliver it and what's taken away, and then the person's understanding of what that means.
>
> Researcher, clinical psychology

Further, the presence of psychotic illness was perceived as a reason to develop appropriate communication strategies and to evaluate carefully the risk-benefit ratio of results communication. Again, a diagnosis of a psychotic disorder was *not*

[20] Thorogood, Adrian, Dalpé, Gratien, and Knoppers, Bartha Maria, 'Return of individual genomic research results: are laws and policies keeping step?', *European Journal of Human Genetics* 27 (4) (2019): 535-546; Kostick et al., *op. cit.*

perceived as a valid reason to withhold information from research participants. At the same time, several researchers argued that genomics represents a more sensitive area compared to neuroscience, mainly because of the cultural discourse surrounding genomic information:

> I suppose there's an extra degree of problem often with genomics, because it's so emotive, and people often seem to feel that genes are destiny, in a way that environment or kind of mediating processes aren't, that's of course less true in some ways. But because of that it's very easy to tell people something that would make them feel doomed, and so I think there are special difficulties that arise from the difference in degree to which that can happen.
>
> Researcher, psychiatry

Despite the fact that recent literature questions the distinction between intended and incidental research findings,[21] researchers in this study still recognised specific obligations when relevant 'incidental' or 'unsolicited' findings emerge from their research. Yet, managing incidental findings was perceived as not particularly problematic. Most researchers recognised that they have a moral obligation to report relevant, clinically-actionable incidental findings, and that research participants have a right (not) to know them. Researchers argued that the most reasonable way to manage incidental findings is to establish an appropriate course of action before the research takes place. The possibility that the research might generate incidental findings should be explained in participant information sheets. Participants should be informed of this possibility and given the opportunity to express their disclosure preferences. Procedures to deal with incidental findings should be described in the research protocol and be subject to REC / IRB scrutiny. Such procedures should focus on shared decision-making among different actors and include the research participant, the family (if this was the participant's preference), and other professionals:

[21] Eckstein, Lisa, Garrett, Jeremy R., and Berkman, Benjamin E., 'A framework for analyzing the ethics of disclosing genetic research findings', *The Journal of Law, Medicine & Ethics* 42 (2) (2014): 190-207.

> Ideally you've already got a protocol in place about how you manage it, you have to be ready for it, […] Often it's about having a clear protocol around how you signpost people, and ensure they get the support they need. Now it's the same with, you know, brain imaging, if you find anything you are expecting is problematic you should have a kind of plan of how you signpost or direct those people to kind of the support or additional checks they need to help them.
>
> Researcher, clinical psychology

Interestingly, most researchers argued that where (i) a pre-determined course of action was clearly described in the research protocol, (ii) this course of action was based on established guidelines, and (iii) the preferences of a capacitous individual were respected, then disclosure of incidental findings would not be a particularly challenging moral dilemma. The interplay among research protocol, REC / IRB scrutiny, and shared decision-making was perceived as well suited to regulate unforeseen circumstances:

> But I think again you would build that into your ethics procedure, so that you would say to any of your potential participants, the study is about this, however, these techniques can also reveal other conditions that, health conditions that might have a bearing on your ability to function. And therefore, you know, you'd make it part of the consent process […]
>
> Researcher, education

3.4.2 Psychosis, bio-information, and mental health care

I asked researchers and health professionals about the clinical translation of neurobiological findings and the moral challenges that may arise from this translation. Participants expressed polarised views. Interestingly, such views correlated more with participants' background—whether this was psychiatry, psychology, nursing, or social work—than with their role as researchers or health

professionals. The current lack of clinical applications, especially with regard to genomics, was perceived as a moral challenge in itself. However, several participants expressed positive views regarding potential future applications particularly with reference to (i) psychosis prevention, (ii) revision of diagnostic categories, and (iii) better treatment options and more targeted clinical triage:

> I think it's got to be into stratification. So, it's got to be into profiling people at first episode of psychosis and really understanding in detail the whole range of different things that are going on and that's on the biological, the psychological and the social level. You've got to be able to say when a young person comes in front of us, this is the pathway you are likely to take, and this is the treatment that is effective for you. At the moment, we give the same package of treatment to everybody, we have no way of sub-dividing essentially. So, that's got to be the way forward. We are still so far off that I think we've got to use all the tools, all the neuroscientific methods we have available to us to try and do that stratification.
>
> Researcher, psychiatry

At the same time, several participants in both groups argued that neurobiology-based diagnostic measures might eventually be harmful. First is the issue of resources. Mental health services were described as structurally under-resourced. Translating new technologies into mental health care might prove difficult because of lack of funding and, at worst, could risk affecting existing resources. Second, researchers highlighted potential risks of over-diagnosis and over-treatment. Several health professionals also noted that misdiagnosis of psychotic illness is part of the history of psychiatry. Hence, it is important to ensure that the translation of neuroimaging and genomics into clinical care does not exacerbate over-diagnosis, but that it is directed towards reducing misdiagnosis. Third, when asked about the potential effects of neurobiology-based diagnostic tools on clinical practice, several health professionals linked the risks of over-diagnosis and over-treatment with the issue of medicalisation:

> But then, that takes away an individual's personal choice to access a service and we may be identifying people who don't actually have a difficulty, have unusual experiences, but they're not distressed by them. So why would we bother them? From my point of view, it wouldn't really be helpful because in most cases people seek help and it's through the assessment of the difficulties that we identify, which services and which interventions may be most helpful.
>
> Health professional, psychotherapist

According to several health professionals, potential harms also include (i) the development of more invasive diagnostic measures, which in turn is linked to risks to privacy and confidentiality, and (ii) the fact that neurobiological information revealing psychosis-risk status might not be actionable, thus increasing the risks of hopelessness and disengagement in patients and service users:

> I think again it's going to depend on the context I think, and on how accurate those predictions might be and then on again what the potential for change would be given you know those risk factors. And, you know if there are likely to be interventions that are useful, otherwise I think the potential for harm probably outweighs the benefit.
>
> Health professional, psychiatrist

Participants also argued that the translation of neurobiological findings into clinical care might be welcomed by practitioners depending on their professional background and on the aetiological model of mental illness to which they refer. Professionals with a medical or psychiatric background could respond positively. Conversely, practitioners whose background is in psychology or social work could react with scepticism, and this could generate tensions within clinical teams. However, several participants highlighted the relevance of constructive interplay within multidisciplinary teams. They argued that such interplay would be vital to ensure that the focus of clinical translation remains improving patient care:

> So there's a really healthy tension I think with the mental health services between the medically-trained colleagues who have very much an appreciation of the biology and the science involved in the development of mental illness and then the psychologically-trained staff who have very much an appreciation of the psychosocial impact on development of mental health problems. And there's a very healthy tension I think between them that actually creates good care for the patients.
>
> Health professional, mental health nurse

Novel diagnostic tools for psychosis could include, for instance, neurobiological markers of psychosis vulnerability and treatment response[22] or machine learning applications to identify psychosis risk and predict psychosis transition or psychotic relapse.[23] I asked professionals what might be the ethical implications of using such tools in clinical care. Again, they described potential benefits and potential harms. Interestingly though, participants did *not* frame the harm-benefit discourse around the evaluation of particular diagnostic tools. Rather, they discussed harms and benefits in relation to how communication of neurobiological information relating to psychosis is *enacted* and in relation to how clinical decision-making may actively involve patients and service users:

> It's all about how that information… how that conversation is had with the service user, you know. 'We want to give you a brain scan because we think it might give us information about your illness' is different to having a conversation with the service user about 'look, there may be different ways of understanding your experiences, we've taken some blood tests, you know, we might be able to offer you a scan, we'd like to do some talking assessments how do you feel about that?' There's different ways of having that conversation with the patient.

[22] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*
[23] Valli, Isabel et al., 'Identifying Individuals at High Risk of Psychosis: Predictive Utility of Support Vector Machine using Structural and Functional MRI Data', *Frontiers in Psychiatry* 7 (2016): 52; Gifford et al., *op. cit.*; Barnett, Ian et al., 'Relapse prediction in schizophrenia through digital phenotyping: a pilot study', *Neuropsychopharmacology* 43 (8) (2018): 1660-1666; Shatte, Hutchinson, and Teague, *op. cit.*

Health professional, mental health nurse

> No, that's the thing, so I think yes I suppose it's how the information that is used isn't it? It might not… it might be used by people who are providing care as a way of preventing people developing serious mental illnesses, and then the information could be used in an adverse way whereas people are discriminated against.
>
> Health professional, mental health nurse

In other words, novel diagnostic tools were perceived as potentially harmful or potentially beneficial in relation to the *degree* of effective communication that is established with the care recipient. This was evident in the discussion around psychosis risk communication. Participants argued that communication of psychosis risk has the potential to increase distress in (asymptomatic) individuals, or even to result in over-treatment:

> And it could… people running away saying 'I don't want to think about this ever, go away, I don't want to see you'. Or, it could have the opposite effect, it could make people over worried and over anxious and be seeking, you know, consults over the very mildest of symptoms. And maybe the over prescription of medications.
>
> Health professional, psychiatrist

Psychosis risk communication should highlight that an increased risk of psychosis does not mean that psychosis transition is inevitable; that psychotic experiences are common in the general population; and that many people are not distressed by them. Overall, several health professionals supported the argument that novel diagnostic tools could be beneficial to patient care *only* if effective clinician-patient communication is established:

> I think it's how you talk to the person and help them to understand that all of our brains have to be different, every last human, and this is how your

> brain actually works, but this is how I can help that brain to give you happiness and a good quality of life.
>
> Health professional, counsellor

3.4.3 Identity, relationships, and the future

I asked both groups how they thought neurobiological explanations of psychosis might relate to Essentialist Thinking (ET) in understanding mental illness and to stigma and labelling. When asked about ET—that is genetic essentialism, or the view according to which specific mental traits emerge inevitably from a genetic 'essence', and neuro-essentialism, which is the same view with reference to neural substrates[24]—most researchers said that they had encountered some form of essentialism within their professional network but that ET was *not* common in patients. Participants in both groups agreed that there is a great variation in how patients understand the aetiology and the nature of psychosis. At the same time many health professionals recognised their responsibility in shaping their clients' views around mental illness:

> […] especially psychiatrists have a great influence over the way people actually think about their illness. So, if they've worked with a psychiatrist that's biologically based in nature then they're more likely to see that their illness is something that's inherent within them. And as an illness, if they've worked with a psychiatrist and mental health practitioners such as nurses that take a much broader view that look at it as a bio/psycho/social model, then they will see that different things cause their illness to come back.
>
> Health professional, mental health nurse

Participants expressed a variety of views about what they thought the relationships between the development of neurobiology and essentialism might entail. According to several participants in both groups, focusing on the genomics of psychosis could

[24] Haslam, *op. cit.*; Heine, Steven J., Cheung, Benjamin Y., and Schmalor, Anita, 'Making Sense of Genetics: The Problem of Essentialism', *Hastings Center Report* 49 Suppl 1 (2019): S19-S26.

increase ET in clients and society. At the same time, many researchers argued that *molecular* genomics could in fact reduce ET, by providing evidence that psychotic disorders are complex conditions and that other risk factors play a significant role in psychosis onset. Participants in both groups argued that neurosciences also have the ambivalent potential to increase or reduce ET, depending on *how* information on neurobiology is communicated. Further, both researchers and health professionals recognised that neurobiological models of mental illness have the potential to be either stigmatising or de-stigmatising. For instance, framing the neurobiology of psychosis within a 'broken brain model' could reinforce stigma. On the other hand, neurobiology could help to reduce social stigma (i) by removing individual responsibility and blame over the illness and showing that mental illness can impair agency, and (ii) by providing a better understanding of the illness and more accurate diagnostic procedures. Interestingly, some professionals refused to describe stigma as linked to aetiological models. They preferred to describe stigma as a social and cultural issue which characterises the diagnostic category of schizophrenia:

> I don't think it's related to stigma, I don't think those explanations affect stigma. I think pre-existing knowledge and misinformation affect stigma. […] Stigma to me is something that's perpetuated by society and not by causation, it's a social difficulty, stigma, not… nothing to do with biological explanations.
>
> Health professional, psychotherapist

Interestingly, several participants in both groups expressed concern over how having access to information on genetic predisposition and brain processes could affect patients and families. Participants argued that neurobiological explanations of psychosis might influence how individuals construct their self-narratives and shape their own identities. This could have positive or negative consequences. On the one hand, most participants agreed that integrating psychosis into one's own identity might have positive consequences and promote resilience. On the other

hand, some researchers highlighted the potential for neurobiological models of psychosis to instil a sense of hopelessness towards recovery:

> And if it's something neuroscientific, then that implies there's not much you can do yourself that can change that. It's something wrong with your brain. It's not something that practising mindfulness is going to help much. You see what I mean? It's quite… It doesn't instil much hope if you've a feeling it's a biological problem.
>
> Researcher, psychiatry

Linked to this argument was the idea, expressed by several health professionals, that neurobiological explanations of psychosis might undermine the sense of *agency* and the potential for *recovery* in patients and service users. Most importantly, participants in both groups argued that promoting a neurobiological understanding of psychosis might influence clients' life choices. Again, this could have positive consequences—if for instance individuals refrain from behaviour that could increase their risk of developing psychosis, such as taking recreational drugs—or negative consequences. Participants expressed concern over the potentially negative, life-limiting influence over clients' life choices. This concern was evident with regard to reproductive choices:

> [It] may impact people's relationships and life choices, so if they feel these are my genes, this is the way I am, it might impact on someone whether to have children or not.
>
> Health professional, care coordinator

Impact on family relationships was also recognised as an area of concern. Participants described the risk that families might assume a paternalistic role whereby a (young) person is seen on an inevitable trajectory towards mental illness and therefore her freedom and autonomy are restricted. Interestingly, health professionals highlighted the risk that promoting a neurobiological understanding

of psychosis might generate family conflicts by instilling feelings of *blame* and *guilt* towards the illness among family members.

Lastly, I questioned health professionals regarding the possibility of having genetic testing for psychosis and schizophrenia in the future. I reminded participants that such testing does not currently exist. I did not specify what *type* of testing would be available in this thought experiment—whether this would be carrier, prenatal, predictive, or diagnostic testing. Interestingly, participants often expressed negative views when they linked genetic testing to the reproductive domain. Most health professionals expressed concern over the possibility to have carrier or prenatal testing. They feared that such tests would negatively condition individuals' reproductive choices:

> If you identified genetic markers, at what point does that end? So, do you test parents before they start a family to see if they're carriers, to advise them that there's a risk that they might pass on a gene to children potentially? That… it's huge.
>
> Health professional, psychotherapist

> […] and the danger is… say if it was part of the test you had during scans in pregnancy, the danger is you would use that information to decide whether you're going to have that child or not, and it's kind of quite a skewed picture.
>
> Health professional, social worker

However, the group of health professionals expressed ambivalent views regarding predictive or diagnostic testing. On the one hand, many professionals feared that genetic testing might generate hopelessness towards recovery, discrimination of individuals who have genetic predisposition to psychosis, and risk of family conflicts due to feelings of blame and guilt. Conversely, other professionals pictured a narrative of empowerment whereby predictive and diagnostic testing might produce personal benefits. According to this narrative, knowing about

genetic predisposition could help individuals to direct their life choices towards psychosis *risk reduction*:

> I think it's going to depend on their own health beliefs. Some people may view it as enlightening, they may feel informed, they may feel that yes, they have to make some modifications to their life in order to reduce their risk of developing psychosis.
>
> Health professional, mental health nurse

The potential clinical utility of predictive testing was particularly reaffirmed when asymptomatic or help-seeking individuals have a long family history of mental illness. But again, most participants stressed the importance of clinicians' gate-keeping function in accessing information on genetic predisposition to psychotic illness.

3.5 Discussion

Even though relevant differences persist on the epistemological value attributed to neurobiology across the aetiological divide, this study suggests that the moral challenges of accessing neurobiological information in the context of psychosis reach *far beyond* the traditional dispute between biological and psychosocial approaches to mental illness. Further, this study suggests that while they may differ with regard to the recognition of moral obligations pertaining to their professional role, researchers and health professionals from diverse backgrounds recognise similar accounts of the moral challenges and ethical principles governing the acquisition, communication, and use of bio-information with individuals who (may) suffer from psychosis. The key message that emerged from the interviews is that information around genomic and brain correlates of psychosis, as well as information around psychosis risk status and illness susceptibility is a *powerful tool* in the process through which research participants and care recipients define their identity and establish personal and clinical goals. A growing body of literature recognises the importance of investigating stakeholders' perspectives on the

expansion of psychiatric genomics and the ethical issues thereof,[25] as well as on the translation of neuro-technology in mental health care.[26] This study sits within this debate by describing researches and health professionals' perceived moral responsibility in managing access to bio-information in the context of psychosis, which, among mental health conditions, has historically been one of the most controversially debated across the aetiological divide.[27]

To cite the work of Emily Postan, neurobiological information can be seen as a "tool of narrative self-conception".[28] In the case of psychosis this tool has profound implications on how individuals see themselves, for instance as being inherently flawed or able to integrate psychotic experiences in their self-image; on how individuals see their actions and choices as restricted by their biological essence or as open to hope, resilience, and recovery; and on how individuals shape their interactions, for instance in establishing conflicting or harmonious relationships with care providers and family members. This argument resonates with psychological theories around *narrative identity* and its relevance for mental health.[29] Further, while the development of a coherent personal narrative is essential to mental health, it acquires particular prominence in the context of psychosis.[30] Within this framework, the present study suggests that the *acquisition* of neurobiological information may be morally relevant and yet, not particularly problematic—so long as it respects the rights, dignity, and autonomy of research participants and care recipients. Conversely, the way in which neurobiological information operates as a tool of narrative self-conception depends on *how* neurobiological information is communicated and enacted, in research as in clinical care.

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[25] Lawrence, Ryan E. and Appelbaum, Paul S., 'Genetic testing in psychiatry: a review of attitudes and beliefs', *Psychiatry* 74 (4) (2011): 315-331; Sundby, Anna et al., 'Stakeholders in psychiatry and their attitudes toward receiving pertinent and incident findings in genomic research', *American Journal of Medical Genetics Part A* 173 (10) (2017): 2649-2658.

[26] Borgelt, Emily, Buchman, Daniel, and Illes, Judy, 'Neuroimaging in mental health care: voices in translation', *Frontiers in Human Neuroscience* 6 (2012): 293; Illes et al., 'In the mind's eye: provider and patient attitudes on functional brain imaging', *op. cit.*

[27] Bentall, *Madness Explained. Psychosis and Human Nature*, *op. cit.*

[28] Postan, *op. cit.*

[29] McAdams, Dan P. and McLean, Kate C., 'Narrative Identity', *Current Directions in Psychological Science* 22 (3) (2013): 233-238.

[30] Ben-David, S. and Kealy, D., 'Identity in the context of early psychosis: a review of recent research', *Psychosis* 12 (1) (2019): 68-78; Lysaker, Paul Henry and Lysaker, John Timothy, 'Narrative Structure in Psychosis', *Theory & Psychology* 12 (2) (2002): 207-220.

Let me explain this further. As one participant in this study poignantly phrased it, “it’s all about delivery!” [Researcher, clinical psychology]. Substantive moral challenges—that is, occurrences that are perceived as morally complex—emerge when information around genetic predisposition and brain processes is delivered to research participants and care recipients. Researchers and health professionals supported the argument that substantive moral challenges do not arise from how neurobiological information is *acquired*, provided that ethical safeguards—such as informed consent of capacitous individuals, thorough ethical review, and specific guidelines to deal with unforeseen situations such as incidental findings—are put in place. Conversely, they suggested that substantive moral challenges arise from how neurobiological information is communicated, how information shapes clinical interventions and social interactions, and how information affects self-narratives and decision making. I shall briefly explain how this argument relates to the three thematic areas presented in the results.

First, research ethics. Neither researchers nor health professionals expressed relevant concerns around traditional research ethics issues. These were seen as important but largely unproblematic. Researchers and health professionals distanced themselves from paternalistic, population-based accounts of vulnerability.[31] They framed access to neurobiological research around autonomy and non-discrimination. This resonates with a body of literature which highlights how individuals who suffer from mental illness often insist upon their equal right to participation.[32] Further, most researchers in this study recognised that vulnerability can stem from certain factors—such as age, capacity to consent, or clinical status—but did not believe individuals who suffer from psychosis require additional protection *only* because of their diagnosis. This echoes Bracken-Roche and colleagues’ critique of class membership accounts of vulnerability as ill-suited to represent the reality of psychiatric research participants.[33] Again, researchers recognised that they have a moral obligation to return aggregate or even individual

[31] Bracken-Roche et al., 'The concept of 'vulnerability' in research ethics: an in-depth analysis of policies and guidelines', *op. cit.*; Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*

[32] DuBois, James M., 'Justice in Recruitment and Research', *Ethics in Mental Health Research* (New York: Oxford University Press, 2008), 123-150.

[33] Bracken-Roche, Bell, and Racine, *op. cit.*

results where participants wish to know them, and that they have a duty to communicate clinically actionable incidental findings[34] while avoiding therapeutic misconception.[35] To summarise, traditional research ethics issues were perceived as easily solvable via REC / IRB review, professional guidelines, and shared decision-making. At the same time, the 'delivery' of neurobiological information to research participant was problematised. In other words, *whether* to enrol individuals with psychosis in neurobiological research or whether to disclose results were perceived as morally unproblematic. Conversely, *how* to communicate neurobiological findings was perceived as morally problematic.

Second, participants pictured a similar narrative about the translation of neuroscience and genomics into mental health care. Health professionals framed the discourse around the harms and benefits of neurobiology-based diagnostic tools in relation to the *degree* of effective communication established with care recipients. This was evident with reference to psychosis-risk communication and psychosis prediction.[36] Health professionals expressed concerned about having a positive or negative impact on their clients' (developing) identity. Whether such an impact might be positive or negative depends on how neurobiological information is 'delivered'—that is, communicated or used—in the clinical encounter. This study suggests that delivering neurobiological information on psychosis in clinical care can *potentially* be beneficial or harmful to the development of clients' identity. The *actual* effect on clients' identity depends on the modalities of such delivery. For instance, Kong at al. have highlighted the risk that genomic medicine might promote fatalism towards mental illness, which in turn could undermine patients' agency and autonomy.[37] This argument closely relates to the idea of hopelessness described by health professionals in this study. Whether delivering information on genomics and brain processes might promote fatalism and instil a sense of

[34] Jarvik, Gail P. et al., 'Return of genomic results to research participants: the floor, the ceiling, and the choices in between', *The American Journal of Human Genetics* 94 (6) (2014): 818-826; Lazaro-Munoz et al., *op. cit.*

[35] Burke, Wylie, Evans, Barbara J., and Jarvik, Gail P., 'Return of results: ethical and legal distinctions between research and clinical care', *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 166C (1) (2014): 105-111.

[36] Mittal, Vijay A. et al., 'Ethical, Legal, and Clinical Considerations when Disclosing a High-Risk Syndrome for Psychosis', *Bioethics* 29 (8) (2015): 543-556; Corsico, 'The risks of risk. Regulating the use of machine learning for psychosis prediction', *op. cit.*

[37] Kong, Dunn, and Parker, *op. cit.*

hopelessness or, conversely, be positively incorporated in a client's personal narrative depends on *how* such information is used. Again, this resonates with recent literature on interview-based risk assessment and psychosis prediction, which highlights the importance of developing appropriate communication strategies and of promoting a narrative of empowerment against a sense of hopelessness in care recipients.[38]

Third, this study suggests that the relations between neurobiological information and identity are much broader than the ethico-legal implications captured by the discourse around benefits and harms in research and care. For instance, it is not clear whether biogenetic explanations of psychosis might increase or reduce stigma and self-stigmatisation, as the relations between biogenetic explanations, essentialist thinking, and stigma are extremely complex.[39] Participants in this study corroborated this view. However, they emphasised researchers and clinicians' responsibility in shaping views around psychosis and in contrasting stigma.[40] Further, health professionals suggested that there are situations in which having predictive genetic testing could have clinical or personal utility by directing life choices towards risk reduction, particularly when individuals who could undergo predictive testing have a family history of mental illness. Rather than establishing precise criteria to evaluate the utility of psychiatric genetic testing, such framing highlights practitioners' responsibility in mitigating the potentially negative ramifications of genetic testing for patients and families[41] while promoting (non) medical benefits which could result from predictive testing.[42] Overall,

[38] Cassetta, Briana D. and Goghari, Vina M., 'Ethical Considerations of Screening and Early Intervention for Clinical High-Risk Psychosis', *Ethics & Behavior* 25 (1) (2015): 1-20; Mittal et al., *op. cit.*

[39] Angermeyer, Matthias C. et al., 'Biogenetic explanations and public acceptance of mental illness: systematic review of population studies', *British Journal of Psychiatry* 199 (5) (2011): 367-372; Spriggs, Merle, Olsson, Craig A., and Hall, Wayne, 'How will information about the genetic risk of mental disorders impact on stigma?', *Australian and New Zealand Journal of Psychiatry* 42 (3) (2008): 214-220; Illes et al., 'In the mind's eye: provider and patient attitudes on functional brain imaging', *op. cit.*; Racine, Eric et al., 'Public Discourse on the Biology of Alcohol Addiction: Implications for Stigma, Self-Control, Essentialism, and Coercive Policies in Pregnancy', *Neuroethics* 8 (2) (2015): 177-186.

[40] Illes, Judy et al., 'Neurotalk: improving the communication of neuroscience research', *Nature Reviews Neuroscience* 11 (1) (2010): 61-69.

[41] Appelbaum and Benston, *op. cit.*

[42] Manzini, Arianna and Vears, Danya F., 'Predictive Psychiatric Genetic Testing in Minors: An Exploration of the Non-Medical Benefits', *Journal of Bioethical Inquiry* 15 (1) (2018): 111-120.

practitioners' gate-keeping function seemed to be constrained by their perceived moral obligation to ensure that neurobiological information on psychosis can positively affect clients' self-narratives and personal identities.

3.5.1 Limitations

This study is situated in the domain of consultative approaches to empirical bioethics as it constitutes what De Vries has called descriptive ethics or sociology *in* bioethics.[43] No strong normative claims are grounded in the study results. Yet, as medical technologies are translated into psychiatry, providing a snapshot of the moral life of the actors who must deal with this translation can help bioethicists to frame the normative discourse around ethical principles and moral obligations.[44] This article has two limitations. First, it provides a qualitative overview, but given the nature of purposive sampling the results cannot be generalised to the population of researchers and mental health professionals. The decision to adopt purposive sampling was based on the study rationale, which was to investigate a *variety* of professional viewpoints across the aetiological divide at the expenses of generalisability. The second limitation relates to bias in the perception of moral challenges. Professional backgrounds as reported in the demographics and the cultural *milieu* surrounding participants—recruitment took place in community services and in universities in England—likely influenced perception of moral challenges. I believe that situating participants' perception of moral challenges within a specific social context does *not* account to evidencing bias in participants' views. Rather, it highlights that moral principles and obligations are often embedded within a person's lived experience, and this experience might be of epistemic value for empirical bioethics.[45] I believe that these limitations do not invalidate the study results and that declaring them can better situate the analysis.

[43] Davies, Ives, and Dunn, *op. cit.*; De Vries, *op. cit.*
[44] Holm, *Ethical problems in clinical practice. The ethical reasoning of health care professionals*, *op. cit.*; Kon, *op. cit.*
[45] Singh, Ilina, 'Evidence, Epistemology and Empirical Bioethics', in Jonathan Ives, Michael Dunn, and Alan Cribb (eds.), *Empirical Bioethics. Theoretical and Practical Perspectives* (Cambridge: Cambridge University Press, 2017), 67-83.

3.6 Conclusions

Several scholars argue that translating neuroimaging and genomics into psychiatry is imperative, given the burden of mental illness on population health.[46] Conversely, psychosocial researchers often criticise the expansion of neurobiological approaches to psychosis on ethical and even political grounds.[47] As an exercise of aetiological neutrality, this study suggests that the ethical implications of biomedical innovation in psychiatry may go beyond this, even though extremely important, normative issue. More precisely, this study suggests that the ethical ramifications of accessing neurobiological information in the context of psychosis reach far beyond the sound conduct of clinical research and the ethical translation of research findings in mental health care. Provided that these two activities are carried out by respecting the rights, dignity, and autonomy of those who (may) suffer from psychosis, the actors who perform such activities—that is, researchers and mental health professionals—are likely to recognise that moral obligations towards their clients extend to the *identity impacts* that accessing and using neurobiological information can have in the context of psychosis. As the very actors who operate this tool of narrative self-conception, researchers and mental health professionals will need ethical guidance on how to operate such a powerful instrument.

Researchers and health professionals share a moral responsibility in shaping views around mental illness and recovery. Recognising this responsibility might be a first step towards ensuring that they can face the moral challenges of their professional role. First, it will be important to implement non class-membership accounts of vulnerability[48] which must balance the need to protect individuals from the risks of research participation with the demand for fair access to research, and the respect of the autonomous choices of those (capacitous) individuals who wish to take part in research, access results, and know incidental findings. Second,

[46] Insel, 'Translating scientific opportunity into public health impact: a strategic plan for research on mental illness', *op. cit.*; Kapur, S., Phillips, A. G., and Insel, T. R., 'Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it?', *Molecular Psychiatry* 17 (12) (2012): 1174-1179.
[47] Read, Haslam, and Magliano, *op. cit.*
[48] Bracken-Roche, Bell, and Racine, *op. cit.*; Luna, 'Identifying and evaluating layers of vulnerability - a way forward', *op. cit.*

ensuring that the translation of neuroimaging and genomics into mental health care is beneficial to patients will require health professionals to reflect not only on whether to disclose neurobiological information, but also on *how* this is communicated and *how* it might shape clinical decision-making and social relationships. Third, if neurobiological information is a tool of narrative self-conception, it will be important to develop appropriate guidance on how to use such a tool so that having access to neurobiological information may be beneficial and not detrimental to the development of individual self-narratives. A tool is often morally neutral but can acquire a moral connotation from the ways in which it is used. The way in which individuals who (may) suffer from psychosis construct their self-narratives, define their own identities, and cultivate social relationships is vital to their recovery journey.[49] Hence, reflecting on how having access to information on genetic predisposition and brain processes can affect people's narratives will be vital in order to ensure that neuroscience and genomics can truly benefit those who experience psychosis. Further research, both normative and empirical, is needed to establish not only whether but also how neurobiological information ought to be delivered in the context of psychosis.

3.7 Declarations

3.7.1 Ethics approval and consent to participate

The ELSI-NAPS study was granted favourable ethical opinion by North West – Greater Manchester South Research Ethics Committee, REC reference number: 17/NW/0315. All participants provided written informed consent prior to taking part in the study.

[49] Ben-David and Kealy, *op. cit.*; Henderson, Anthony R. and Cock, Alan, 'The responses of young people to their experiences of first-episode psychosis: harnessing resilience', *Community Mental Health Journal* 51 (3) (2015): 322-328.

3.7.2 Consent for publication

The article contains aggregated anonymised demographic data and anonymised quotations from participants in the ELSI-NAPS study. All participants provided written consent to the use of information about them in anonymous form to support other research in the future. All participants also provided written consent to the use of anonymous quotations collected for the study in scientific publications.

3.7.3 Availability of data and materials

The datasets generated and analysed during this study are not publicly available because they contain information that could compromise the privacy of research participants. The data may be made available by the corresponding author [PC] upon a reasonable request from a bona fide researcher in order to validate the reliability of data analysis.

4. ARTICLE THREE | "We're not moving forward". Carers' demand for novel research and effective interventions for psychotic disorders

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Summary

Like the previous article, also this article is based on the assumption that investigating social actors' conceptualisations of moral challenges can help bioethicists to address the ethical issues of technological convergence. The article contributes to answering my thesis research question by investigating the moral world of another group of actors: carers of a person suffering from psychosis. How can we ensure that technological convergence may truly benefit, and not harm, people who suffer from psychosis? Carers' responses to this question were emotionally loaded and epistemically rich. The carers I spoke to were angry at how they—and their cared-fors—are currently treated in research and clinical contexts. They hoped that technological convergence and the increased understanding of neurobiology that comes with it might produce new avenues for taking care of people who suffer from psychotic illness. At the same time, they feared that technological convergence might produce more harm than benefits. Carers' main message was that their cared-fors' needs must be properly assessed and met if we wish that technological convergence be beneficial. Along with researchers and

health care professionals, carers can provide essential insights on how to build an integrated ethics approach to tackle technological convergence in psychiatry because of the role they play in supporting treatment in the community and because of the values that they cultivate.

4.1 Abstract

The lack of access to effective interventions for psychotic disorders places a considerable burden on informal caregivers. At the same time, the converge of clinical neurosciences and next-generation genomics has the potential to transform psychiatric care. This article presents findings from a qualitative study. I conducted focus groups with carers of someone suffering from psychosis. I investigated how carers conceptualise the ethical issues arising from novel neurobiological approaches to psychosis. On the one hand, carers pictured a narrative of hope. They strongly demanded novel research and effective interventions that might help their ill relative to recover and to lead a flourishing life. On the other hand, carers were frustrated at their present situation and feared that technological innovation might produce more harm than benefits. This study suggests that investigating carers' outlook on sensitive ethical issues is vital to ensure that the needs of those who suffer from psychosis are appropriately met.

4.2 Introduction

Psychosis is a state of the mind characterised by delusions, hallucinations, disorganized thinking, and more generally by a loss of contact with reality. Mental disorders that are primarily characterised by psychosis, such as schizophrenia, are termed psychotic disorders.[1] Psychotic disorders are considered to be among the most severe forms of mental illness. After more than a century of confinement of the mentally ill in total psychiatric institutions,[2] in the last decades deinstitutionalisation and the development of community mental health services have produced relevant social changes in western societies. Yet, the lack of access to effective interventions for psychotic disorders and the burden on informal caregivers are still striking.[3]

As a response to such hindrances to effective mental health care, the past decades have seen a tremendous increase in research into the neurobiology of schizophrenia. The development of clinical neurosciences and their application to psychiatry have helped researchers to unveil the structural and functional processes behind disrupted brain activity in psychotic disorders.[4] The expansion of next-generation sequencing is leading the way towards a greater understanding of the genetic bases and molecular architecture of psychotic disorders.[5] More importantly, neuroscientific and genomic approaches to psychosis are increasingly intertwined because of technological convergence.[6] The converge of neuroscience, next-generation genomics, and data science could soon transform the care of those who suffer from psychosis by helping to redesign diagnostic categories, by supporting

[1] American Psychiatric Association, *op. cit.*
[2] Goffman, Erving, *Asylums. Essays on the social situation of mental health patients and other inmates* (London: Penguin Books, 1991/1961).
[3] Fleischhacker, W. Wolfgang et al., 'Schizophrenia--time to commit to policy change', *Schizophrenia Bulletin* 40 Suppl 3 (2014): S165-S194.
[4] Fusar-Poli, Borgwardt, and McGuire (eds.), *op. cit.*; Howes, Oliver, McCutcheon, Rob, and Stone, James, 'Glutamate and dopamine in schizophrenia: an update for the 21st century', *Journal of Psychopharmacology* 29 (2) (2015): 97-115.
[5] Corvin, A., Ormond, C., and Cole, A. M., 'Genomics of schizophrenia', in Bernhard T. Baune (ed.), *Personalized Psychiatry* (San Diego: Academic Press, 2020), 173-186.
[6] Corsico, Paolo, 'Psychosis, vulnerability, and the moral significance of biomedical innovation in psychiatry. Why ethicists should join efforts', *Medicine, Health Care and Philosophy* 23 (2) (2020): 269-279.

the development of effective interventions, and by ameliorating risk assessment and clinical prediction.[7]

In this article, I use the word 'neurobiology' to indicate the convergence of neuroscience and genomics in tackling psychosis. Potential clinical benefits to be gained from an increased understanding of the neurobiology of psychosis are easy to describe. Yet, what ethical challenges arise from this endeavour? Participant recruitment in mental health research has historically raised many ethical issues.[8] The issue of mental capacity in research and care is longstanding.[9] Further, complex ethico-legal concerns arise regarding the management of neurobiological information in the context of mental illness, such as return of results to research participants,[10] or disclosure of unsolicited findings in neuroimaging research.[11]

At the same time, treatment in the community often means that the relatives of those who suffer from psychotic illness—many times their parents—take on a substantial caregiving role. Mental health carers are an essential component of the community treatment model in psychiatry.[12] An increasing body of literature has started to investigate carers' experiences of caring for a person suffering from psychosis.[13] However, carers' perspectives on the expansion of neurobiological approaches to psychosis and the ethical issues thereof remain largely unexplored.

4.2.1 Study aim

This article presents results from a qualitative study. I investigated how mental health carers conceptualise the ethical issues that arise from the implementation of neurobiological approaches to psychosis and from technological innovation in psychiatry. More specifically, I investigated how carers perceive issues around

[7] Insel, 'Translating scientific opportunity into public health impact: a strategic plan for research on mental illness', *op. cit.*; Shatte, Hutchinson, and Teague, *op. cit.*
[8] DuBois, *Ethics in Mental Health Research. Principles, Guidance, and Cases*, *op. cit.*
[9] Appelbaum, Paul S., 'Decisional Capacity of Patients With Schizophrenia to Consent to Research: Taking Stock', *Schizophrenia Bulletin* 32 (1) (2006): 22-25.
[10] Lazaro-Munoz et al., *op. cit.*
[11] Racine and Illes, *op. cit.*
[12] Cree, Lindsey et al., 'Carers' experiences of involvement in care planning: a qualitative exploration of the facilitators and barriers to engagement with mental health services', *BMC Psychiatry* 15 (1) (2015): 208.
[13] Young, Lisa et al., 'Exploring the Experiences of Parent Caregivers of Adult Children With Schizophrenia: A Systematic Review', *Archives of Psychiatric Nursing* 33 (1) (2019): 93-103.

three areas: (i) ethical issues in clinical research on the neurobiology of psychosis, (ii) ethical issues in clinical translation of neurobiological findings, and (iii) impact on patient care and family dynamics.

4.3 Methods

I conducted three focus groups as part of a larger qualitative study entitled ELSI-NAPS (Ethical, Legal and Social Issues in Novel Neurobiological Approaches to Psychosis and Schizophrenia: A Qualitative Study). The study was reviewed and granted ethical approval by North West – Greater Manchester South Research Ethics Committee, REC reference number: 17/NW/0315. Inclusion criteria to take part in the focus groups were: (i) being aged 18 years or above; (ii) acting as carer / legal guardian of a psychiatric patient or service user with a diagnosis of psychotic disorder or schizophrenia; (iii) being a first or second-degree relative, spouse, or civil partner of the patient or service user. With reference to the COREQ criteria my personal characteristics as chief investigator, focus group moderator, and author of this article are: doctoral student in bioethics, male, with training in qualitative health research.[14]

4.3.1 Recruitment and participants

I used purposive sampling to identify potential participants via two routes.[15] First, posters were placed in physical noticeboards across community mental health services in Greater Manchester Mental Health NHS Foundation Trust. Second, the study was presented at meetings of mental health carers groups in Greater Manchester. Individuals interested in the study were invited to contact me. I had no relationships with potential participants prior to recruitment. Potential participants were screened for eligibility and, if eligible, they were sent a participant information sheet and were invited to take part in one focus group. When at least four

[14] Tong, Allison, Sainsbury, Peter, and Craig, Jonathan, 'Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups', *International Journal for Quality in Health Care* 19 (6) (2007): 349-357.
[15] Battaglia, *op. cit.*

participants had confirmed their availability a date was set and a focus group organized. Fifteen participants were recruited between July 2018 and January 2019. Each participant took part in only one focus group. Three focus groups were held with four, five, and six participants respectively. Group size was kept relatively small for two reasons: (i) in order to facilitate in-depth discussion and allow all participants to talk about their personal experiences, and (ii) because the resources available for recruitment were limited as the study was conducted as part of my doctoral studies.

All participants provided written informed consent and completed a short demographic questionnaire prior to the focus group. They were offered a £20 voucher as an incentive to their participation. Participants could have their travel expenses reimbursed if they wished so. Demographics are presented in table 1. Almost all participants were women and most were parents of the patient or service user. The most common diagnosis was (paranoid) schizophrenia. In other words, the majority of participants were mothers of a person suffering from schizophrenia. This fact may constitute gender bias in participant recruitment. However, recent literature has highlighted gender imbalance in family caregivers of schizophrenia patients. For instance, Awad and Voruganti note how surveys in the US show that up to 82% of schizophrenia carers are female, with 90% of them being mothers.[16] Gender imbalance in family caregiving was also reported in a recent systematic review of qualitative studies[17] and in qualitative research exploring the views of carers in the UK.[18]

[16] Awad, A. George and Voruganti, Lakshmi N. P., 'The burden of schizophrenia on caregivers: a review', *PharmacoEconomics* 26 (2) (2008): 149-162.
[17] Young et al., 'Exploring the Experiences of Parent Caregivers of Adult Children With Schizophrenia: A Systematic Review', *op. cit.*
[18] Lloyd, Joanne et al., 'Treatment outcomes in schizophrenia: qualitative study of the views of family carers', *BMC Psychiatry* 17 (2017): 266.

Table 1. Demographics

	Age	Gender	Education	Diagnosis of cared-for	Relationship with cared-for
Carers *n*=15	[49-76] Median=66 Mean=66.0	F=14 (93.3%) M=1 (6.7%)	Primary education=1 GCSE=5 A-Levels=3 Undergrad. degree=4 Postgrad. degree=2	Schizophrenia=7 Paranoid schizophrenia=4 Psychotic disorder=1 Bipolar disorder=1 Borderline personality disorder=1 Prefer not to disclose=1	Parent=12 Spouse=2 Sibling=1

4.3.2 Data collection

Focus groups took place in public meeting rooms that were hired *ad hoc*. Each focus group lasted for approximately one and a half hour. I used a focus group guide that was not amended across different sessions to comply with REC requirements. The focus group guide is presented in Appendix C. I acted as moderator of the focus groups. A second researcher was present at the venues to assist the author in welcoming participants and in taking field notes. The focus groups were audio recorded. I transcribed the audio recordings *verbatim*. Transcripts were anonymised to ensure confidentiality and pseudonyms are used in this article. Transcripts were not returned to participants for comments and corrections.

4.3.3 Case vignette: The story of Anna, David, and Tom

I used a case vignette during the focus groups.[19] A printout of the vignette was given to participants after approximately 30 minutes since the focus group had started. Therefore, not all themes discussed in the results emerged in response to the vignette. The quotes that refer to the vignette are clearly identified in the results. Given the relevance of the vignette to data generation, I report the vignette below.

[19] A slightly modified version of this case vignette has already been presented as a case study in Article one, section 2.4 above.

Instructions to participants: we are going to describe a scenario to you about a family involved with mental health services and clinical research. Please, read the story and think about what you would do:

Anna and David live in Bolton, Greater Manchester. They have been married for over 20 years. Anna works as a nurse in a local hospital. David occasionally works as a carpenter. He has a history of mental health problems, and has received a number of diagnosis in the past 10 years, including schizoaffective disorder and schizotypal personality disorder. However, he has not been relapsing for the past 18 months. Anna and David have a son, Tom, aged 17. Tom has always done very well in school. He has friends and enjoys playing football and going to concerts. However, in the last year he has been very distressed. His school grades have worsened. He stopped seeing his friends, and he spends a lot of time alone. The family GP[20] has recommended that Tom engage with the local early intervention team. He has received an assessment at the early intervention service, and the clinical psychologist says that Tom is at risk of developing psychosis. A clinical research team approaches Tom and Anna. They offer that Tom be included in a trial, in order to monitor his possible transition to psychosis. Tom would be given a smartphone, which would monitor his activities for the next 6 months. Over the next 6 months, Tom will have to attend a hospital visit once a month for neuroimaging scans. The research team says that this would allow for a better understanding of Tom's condition. In addition, a blood test is available, should Tom decide to do it, in order to assess Tom's genetic risk to develop a psychotic disorder. What would you do if you were Tom? What would do if you were Anna? What would you do if you were David?

[20] In United Kingdom, the acronym GP stands for General Practitioner, who is the family doctor.

4.3.4 Data analysis

Transcripts were analysed in a stepped thematic analysis process to identify recurring themes and to organise the data in a structured format.[21] After a first reading of the transcripts, I developed initial codes that captured the arguments expressed by participants. A first coding structure was developed and transcripts were coded without the use of data analysis software. In a subsequent phase, a second researcher independently reviewed the coding structure against one of the three transcripts to ensure reliability. The coding structure was revised to incorporate the reviewer's comments and a coding manual was developed. The coding structure and manuals were then re-reviewed by the second researcher and by a third researcher and consensus was reached. The transcripts were then transferred to NVivo 11 and were coded using the revised coding structure and manual. Some codes were eventually adjusted during this process. After coding all the transcripts, I wrote the present article. The final coding structure / thematic map may be seen in table 2. The final coding manual is presented in Appendix D.

[21] Braun and Clarke, *op. cit.*

Table 2. Coding structure / Thematic map

Anger
Frustration
At medical profession
At research
Lack of social support
Coercion and moral distress
Expert role of carers
Stigma
Blame on parents for illness
Carers' shame / fear of social judgement
Experiences of discrimination
Stigma and fear related to diagnosis
Frustration at 'politically correct'
Media as drive of social stigma
Need for education on social stigma
Stigma and neurobiology
Research in general can reduce stigma
Neurobiology could reduce stigma by removing blame
Understanding of illness
Psychosis is (not) an illness
Schizophrenia just a collection of symptoms
Right understanding is biological / biopsychosocial
Diagnostic system is flawed

Hopes
Need for effective intervention
Timely and accurate diagnosis
Effective medication
Medication is currently trial and error
Neurobiology may support accurate prescription
Effective prevention
Prediction useful only if intervention available
Strive for knowledge / understanding of illness
Research has vital relevance
Fair access to research / treatment
Peer-support groups are vital to carers
Communication
Detailed information on research to carers
Careful communication (on research) with participants
Confidentiality as a barrier
Effective communication with mental health professionals
Benefits of psychosis prediction / risk identification
Impact on patient's life choices
Extension of individual choices
Increased hope towards recovery if effective intervention

Table 2 (continued). Coding structure / Thematic map

Fears
Resources
No money for new technologies
Poor treatment has societal costs
Harms of psychosis prediction / risk identification
Prevention (prediction) of schizophrenia is not possible
Risk of medicalisation and over-diagnosis
Burden on (young) individuals / iatrogenic effect
Young people difficult to engage in research

4.4 Results

Carers' role in taking care of a person suffering from a psychotic disorder—who is often a son, a daughter, or a close relative—is an intense and emotional experience.[22] For this reason, conducting focus groups with this population presents specific practical challenges. Carers spoke about their experiences and described the problems they face in the everyday practice of caring for their ill relative. They often did so while answering the questions they were asked. More precisely, participants tackled the issues under investigation by embedding their reflections within their personal narratives. This phenomenon has been reported in other qualitative studies with similar populations.[23] Participants who shared similar narratives of caring for a person suffering from mental illness often directed group discussion towards their shared experiences. Rather than constituting a limitation, this fact allowed me to answer the research question by providing context-rich personal narratives.

The main message that emerged from the focus groups was one of ambivalence. On the one hand, carers pictured a narrative of *anger* towards their present situation. Frustration at the medical and research professions, experiences of media-fuelled social stigma, and occurrences of moral distress were commonly

[22] McAuliffe, R., O'Connor, L., and Meagher, D., 'Parents' experience of living with and caring for an adult son or daughter with schizophrenia at home in Ireland: a qualitative study', *Journal of Psychiatric and Mental Health Nursing* 21 (2) (2014): 145-153; Young et al., 'Exploring the Experiences of Parent Caregivers of Adult Children With Schizophrenia: A Systematic Review', *op. cit.*

[23] Wainwright, Laura D. et al., 'What do relatives experience when supporting someone in early psychosis?', *Psychology and Psychotherapy* 88 (2015): 105-119: 107.

reported. On the other hand, carers pictured a narrative of *hope* for the future. They strongly demanded novel research and effective interventions which might help their cared for to recover and to lead a flourishing life, as well as support carers in fulfilling their role without being overwhelmed by it. Participants endorsed a biopsychosocial model of psychosis and recognised the importance of neurobiological research in producing novel interventions and effective prevention. Yet, they were ambivalent in describing how technological innovation might be beneficial to patient and service users. Carers expressed *fears* of how technological innovation might exacerbate common ethical issues in mental health.

I describe the themes that emerged from the focus groups along three emotional axes: anger, hope, and fear. The themes identified are:

1. Anger: frustration, stigma, and understanding of illness.
2. Hopes: need for effective intervention, strive for knowledge, communication, and benefits of psychosis prediction / risk identification.
3. Fears: resources, harms of psychosis prediction / risk identification.

4.4.1 Anger

The most common reaction of participants upon being asked about neurobiological research and technological innovation was a sense of *frustration* towards the medical profession:

> P9: I know they've got the best brain scanner in, um, I mean it's Cardiff or somewhere, in the all of Europe, um but here in [omitted] we're not moving forward, we're not just standing still, we're moving backwards, we are just ticking all the boxes, and, as to diagnosis, using old medications […]

> P13: And I think, yeah, you can look at genetics, you can look at brain scans, you can look at social, whatever, you can look at all that stuff, but basically, what we need is an effective mental health service. And I don't think you got it.

The same level of frustration was expressed with regard to research. Carers were mostly dissatisfied with the limited impact of neurobiological research on clinical practice:

> P14: […] the money that's put into, into, into research with drugs. Incredible! But we need research into what works, what doesn't work, what is, what is wrong! What it's got, but. Just to start, just to give people drugs…

Carer's frustration was exacerbated by the lack of social support available to them and their relatives, and by experiences of coercion and involuntary hospitalisation. In addition, carers felt that they have a specific 'expertise by experience' in identifying their relatives' care needs. However, this expertise is mostly ignored by the medical profession:

> P9: And, I, find, that the only thing that keeps me relatively sane, not completely, is the group, and that's because we are the only ones that know, we are all in the same boat, and we are the only ones that understand. Even the researchers, the psychiatrists, the doctors, nobody understands more than a mental health carer, what it's like to care for somebody with a severe mental illness.

Social stigma attached to psychosis and schizophrenia was mentioned as a common ethical issue. Carers described how social stigma is related to the diagnosis of their ill relative and reported experiences of discrimination, shame, and fear of social judgement. Interestingly, many participants complained that the cultural context in which they live often *blames* parents for their children's illness. In one occasion, participants explicitly linked this phenomenon to 1960s psychosocial theories of illness aetiology developed by scholars such as R. D. Laing:[24]

[24] An account of R. D. Laing's theory about the nature of mental illness in relation to the family can be found in Laing, Ronald D. and Esterson, Aaron, *Sanity, Madness, and the Family. Families of Schizophrenics* [2nd edition] (London: Penguin Books, 1986/1964).

P6: Who was this nut job who was saying that it's all the parents' fault? You know, our friend, what's his name?

P2: Oh yeah, there's, what, after Freud it was…

P6: It's a Freudian, a Freudian… I can't remember his name, I don't want to remember his name, cause he was so destructive, when I thought, [swears], if those people are in charge of helping my son, God help him. It was shocking that someone could be so ignorant and so biased.

[…]

P2: Is it T. Laing or R. D. Laing. Yeah. He's the guy? He's the guy [other people agree]. And it's so primitive now. It's so bloody primitive.

Carers argued that stigma is also fuelled by the media's portrayal of mental illness and of violent crimes involving individuals suffering from schizophrenia. They argued that education is the most appropriate way to deal with stigma. In addition, when asked about the role of biological approaches to mental illness in fuelling or reducing stigma, many participants argued that neurobiology has the potential to reduce stigma by removing blame towards psychotic illness:

P1: But I think what, in answer [to] your question, and what would feel really strongly for me, is, yes, if there was a genetic base to mental illness, I think it would massively reduce stigma. 'Cause what we're saying, this is not people's fault. [Participants agree].

This argument was closely linked to carers' understanding of psychosis. Participants were ambiguous on whether psychosis should be considered an illness. The majority of them argued that psychosis is an illness that must be treated like other physical illnesses. Yet, others were more sceptical of the medical model. At the same time, the two approaches converged around the idea that the term 'schizophrenia' only identifies a collection of symptoms and *not* a discrete condition. More importantly, carers agreed that the current diagnostic system used in psychiatry is inherently flawed:

P14: Imagine if you had diabetes and said 'no, it's not diabetes actually, it's epilepsy'. No no, we're not quite on that, it's like, you kidding me? So, in physical health, it would be taboo to, you know, to get it wrong, to get a diagnosis wrong, imagine getting a diagnosis wrong in physical illness and be treated for that [P12 agrees] and then six months later, yeah, it's much rarer than in mental health, in mental health they're changing diagnoses all the time. Yes, it does happen in physical health.

P13: But, I would say because there's no diagnosis in the first place, it's a, it's a…

P14: It's kind of, what, what…

P13: It's them, it's them imposing labels that don't necessarily fit with the mental health…

P15: it's just tick boxes isn't it, really?

While arguing that the diagnostic system is flawed, most participants seemed to endorse a biopsychosocial model of psychosis whereby biological factors play an important role in the development of psychotic symptoms along with psychosocial factors:

P5: What I would just like to say is, in my opinion, there is a genetic disposition to mental illness. That it doesn't necessarily follow through, but […] So, I do think there is a fam-, a genetic disposition, but I don't think just because one member of the family has it, that it would automatically follow through […]

4.4.2 Hopes

In sharp contrast with feelings of anger towards their present situation, carers expressed *hope* that novel research and technological innovation may bring improvements in the life of their ill relative and support carers in their caregiving role. Carers strived for knowledge and demanded that neurobiological research cast more light on the nature of psychosis:

> P2: And, just because the dopamine, um, research didn't get anywhere, doesn't meant they have to throw it out again and go back to 'abuse'. So, I think, [inaudible], shut up, and do what we're doing, and get in people that are doing the research, taking the time, and getting the evidence, because…my sons deserve that […]
>
> P9: Because that's the only way of moving forward. If, if we don't do research and people get on board more than they are, and, and drag the old stalwarts out of the past into the future.

Carers also demanded better access to research on grounds of fairness towards people who suffer from mental illness if compared to those who suffer from physical illnesses. This argument was linked to the demand for better communication with the medical and research professions. Detailed information on research should be more easily available to carers:

> P2: There's lots of trials going on now, and some of them are really getting somewhere, and you know, we're just not told about them. And, the other thing is well, what's, the, the blood test, for the markers, to see if your young person has got treatment resistant schizophrenia, there are trials going on, and, I know my son was just a little bit too late for the trial because we weren't told about it, or we should have been.

Detailed information on research should be provided to carers and careful communication on research opportunities should be established with their ill relatives, especially when these are young. In a broader perspective, carers demanded better communication between the family and mental health professionals about research opportunities and treatment strategies. The need for effective communication was anecdotally exemplified by carers' tendency to consider confidentiality as a barrier to their caring role:

P12: I recognise that confidentiality is a real issue nevertheless. And that, you know, somebody. My son is entitled to confidentiality…

Moderator: Yeah.

P12: … and handling that is very difficult. The most crude way to handle it is to fend people off and say 'I can't talk to you because is confidential'. Then nobody wins. Including in research and not just, you know.

Moderator: Do people share this view about confidentiality?

P15: Yeah.

P13: Yeah.

P14: Oh yeah. Absolutely.

P15: In a big way [laughs].

P14: And it is a big way because I think, sorry, sorry [P15], I think, I think because we see our loved ones in the most vulnerable position, and there's nothing we can do about it because of confidentiality.

Overall, carers' strongest hope was for the development of effective interventions which might help their cared-for to recover and to live a flourishing life. According to carers, three elements would be necessary to achieve this: (i) timely and accurate diagnosis, (ii) effective medications, and (iii) effective prevention. First, diagnoses should be timely and accurate:

P6: Now my son, my son wasn't diagnosed until things went very very bad when he was 18, that's when he really went haywire. But, in a way, in a way his diagnosis was a blessing, because I understood why all this had been going on ever since he was a child. Lot of things happening. Where were the people to identify that?

Second, and most importantly, carers' strongest hope was that neurobiological research and technological innovation might produce interventions that are effective in treating psychotic disorders:

Moderator: What would be the thing that is most needed?

> P14: Well, to find out what causes mental illness [laughs, other participants agree]. You find out what causes it then, you know, then we can get an action plan together about what you can do to treat it.

This includes developing better medications. Antipsychotic medications were generally perceived by carers as too burdensome for their ill relative. Carers described prescription of antipsychotics as a 'trial and error' process carried out by psychiatrists at the expenses of their relatives' quality of life. They hoped that a greater understanding of the neurobiology of psychosis might improve accurate prescription in the future.

Third, particularly when discussing the case vignette, carers expressed hope that effective prevention of psychotic disorders in general, and of crisis events in particular, be put in place:

> P9 [discussing vignette]: So, if I was Tom, yes, I would like to think, knowing what I know now, I would grab everything that was offered to me [participants agree] with a view to stopping anything happening. […] Um, if I was David, I would be pressing my son, 'look at me! Is this what you want for your future? Or, can we stop this happening?'

At the same time, several participants specified that prediction of psychotic illness would be useful *only* if effective intervention was available, thus subordinating accurate prediction to the availability of appropriate intervention:

> P9: If you are going, if you're going to be able to give me something that is going to stop schizophrenia or bipolar or whatever it's going to be, why, do you want to live with that knowledge, um, if there isn't anything positive on the horizon?

Carers recognised that some benefits might derive from psychosis prediction and risk identification when these are supported by novel technologies,

as discussed in the case vignette. Such benefits were generally linked to the extension of individual *choices*, both for patients as for their caregivers:

> P2: Well, it could give us the choices and chances … [one participant agrees] […] I mean, at least, we would have the choice, take the blood test to see if, if you, if you can pass it on, or you've got it, to a different degree. And I mean, at least, they deny us any choices with mental illness. And it is illness, it's not just emotional problems. And, we are just denied choices.

4.4.3 Fears

Not only did carers voice their needs and hopes. Their reaction to future scenarios was ambivalent. Carers feared that technological innovation might exacerbate moral challenges in mental health and eventually produce more harm than benefits. First, participants argued that poor treatment of mental illness has high societal costs, which are often borne by informal caregivers. At the same time, carers were sceptical that technological innovation could be easily implemented in mental health services because of the structural lack of funding:

> P1 [discussing vignette]: but can I just tell, it feels to me cloud cuckoo land that anyone gets that level of service [laughs]; do you know what I mean? [participants agree] And so, it would be wonderful, I mean, you've talked about things and may—when you're in the inside you know where few people get these sorts of treatments, but the sense to me is, there's millions of people banging on the door for help and get turned away, there's people [participants agree], you know what I mean?

Carers also identified a number of other hindrances to the implementation of (research on) technological innovation. Despite expressing their need for effective prevention (as described above), several participants were sceptical that prevention and prediction of psychotic disorders might be even possible. Carers also argued that young people are very difficult to engage in neurobiological research:

> P14: […] when I think about my son's perspective, that's a different bargain. At least, well, I think he's very wary of, of, of anybody that tries to intervene with his way of thinking, at certain times. So, I remember when he was quite young, actually, probably in his early, maybe 18, early twenties, and it was suggested that maybe he goes to some kind of brain scan, and he saw that as a, as a real intrusion. You know, how dare you? You want to pick, literally pick my brains, and examine them.

Further, carers worried about two potential sets of harms when discussing future developments as described in the case vignette. First, carers worried about the risk to medicalise adolescents' behavioural difficulties and to over-diagnose psychotic illness:

> P6 [discussing vignette]: […] Tom being 17, um, I can't really see anything that's, what's wrong with, when you spend time alone when you're an adolescent? It's just about the time, when there's a lot going on, um, you know identity formation, and although I think [clears throat] that a lot of heavy mental constructs are going on at that time. I would actually be careful about exposing Tom to even the suggestion.

Second, carers worried about the burden of (research on) psychosis prediction on young people and about the iatrogenic effect that such burden could have on them:

> P3 [discussing vignette]: So, I mean, it's kind of very tricky especially at age 17. I know, when my son was 17 he didn't realise he had a problem, and 'what am I talking about? You're talking about going to the hospital. Why are the early intervention team here? What you doing, are you trying to lock me up?' It, it's been terrible. Absolutely terrible. So, if he does do it, that's good for him. But I find it very challenging that a 17 year old would volunteer to do it. Um, it'd be good for him if he does but, as I said, and all these things with blood tests, and, how can they afford to do all that? Is he

a guinea pig then in here? Because, I said, he's starting psychosis, he's in transition. His 'possible transition to psychosis' so he's actually being treated for the possibility of having psychosis. The possibility.

P9 [discussing vignette]: I, I think it would make somebody mentally ill [Participants loudly agree]. The stress trigger.

4.5 Discussion

These findings highlight mental health carers' demand for novel research and effective interventions. Yet, what moral challenges arise from the convergence of neuroscience, next-generation genomics, and data science in tackling psychotic illness?

Interestingly, some key topics that characterise the ethics debate were absent from carers' discussion. Carers rarely, if ever, mentioned mental capacity. Those who suffer from psychosis do *not* automatically lack capacity to make decisions on research and care.[25] However, the issue of mental capacity—governed in England and Wales by the Mental Capacity Act 2005—represents the framework that regulates care decisions and access to research in this jurisdiction. Thus, one would expect capacity to play a prominent role in the discussion of ethical concerns. This did not happen. Coercion and involuntary hospitalisation were mentioned by participants, but only in relation to their experiences and to feelings of moral distress. Further, the ethics debate on clinical neurosciences and psychiatric genomics is often focused on how to handle neurobiological information: returning results to research participants,[26] managing unsolicited neuroimaging findings,[27] and data sharing[28] are among the most debated issues in current ethico-legal literature. Such issues were almost absent from carers' discussions in this study.

[25] Appelbaum, 'Decisional Capacity of Patients With Schizophrenia to Consent to Research: Taking Stock', *op. cit.*; Appelbaum, Paul S., 'Clinical practice. Assessment of patients' competence to consent to treatment', *The New England Journal of Medicine* 357 (18) (2007): 1834-1840.
[26] Lazaro-Munoz et al., *op. cit.*
[27] Racine and Illes, *op. cit.*
[28] Information Commissioner's Office, *Big data, artificial intelligence, machine learning, and data protection* (2017).

Why is that so? One possible reason could be the design of this study, which investigated carers' perceptions of moral challenges by asking carers general questions and by reflecting on a case vignette. Carers were not asked directly about the issues mentioned above, and therefore they did not mention them. This is a possibility. A second explanation could be that carers are lay members of the public. They are not ethics and legal experts. Thus, they might not be aware of many complex ethico-legal issues. This is also a possibility. However, a different hypothesis can be grounded in this study's data: carers' narratives may reveal a *different outlook* on the moral challenges of technological innovation in psychiatry. Given the specific viewpoint from which carers reflect and operate, I shall argue that this outlook can be properly understood only by referring to an ethics of care.

The moral life of the mental health carers who took part in this study was dominated by the interplay between anger, hope, and fear. Carers face many challenges in the everyday practice of caring for their ill relative. Some of these challenges and the emotional struggle carers have to endure are well documented in qualitative literature, and they are mirrored in the results presented here. Carers' relationship with mental health professional is often conflictual, and carers feel that their competence is not recognised.[29] Confidentiality is perceived as a barrier to effective communication and as a tool used by the medical profession to exclude carers from treatment decisions.[30] Carers strive for a clear diagnosis and for an increased understanding of psychosis.[31] They demand timely and effective interventions.[32]

The emotional ambivalence—anger, hope, and fear—represents the background against which carers conceptualise ethical issues in technological innovation. I argue that this emotional ambivalence towards technological

[29] Angermeyer, Matthias C., Schulze, Beate, and Dietrich, Sandra, 'Courtesy stigma--a focus group study of relatives of schizophrenia patients', *Social Psychiatry and Psychiatric Epidemiology* 38 (10) (2003): 593-602: 595; Cree et al., *op. cit.*, 6-8.
[30] Askey, Ryan et al., 'What do carers of people with psychosis need from mental health services? Exploring the views of carers, service users and professionals', *Journal of Family Therapy* 31 (3) (2009): 310-331: 312; Wainwright et al., *op. cit.*, 111.
[31] Wainwright et al., *op. cit.*, 109.
[32] Askey et al., *op. cit.*; Hickman, Gareth et al., 'The experiential impact of hospitalisation: Parents' accounts of caring for young people with early psychosis', *Clinical Child Psychology and Psychiatry* 21 (1) (2016): 145-155.

innovation has *epistemic* value: it allows us to identify (some of) the care needs of those who suffer from psychotic illness.

4.5.1 Care as practice and value

The epistemic value of the results of this study can be properly recognised only within an ethics of care. The practice of care starts with the recognition of the other's needs. Caring implies "taking the concerns and needs of the other as the basis for action."[33] How can the convergence of neuroscience, next-generation genomics, and data science be beneficial to those who suffer from psychosis? Participants in this study suggested that technological innovation could be beneficial *only* if we identified the real caring *needs* of those who suffer from psychosis. They recognised the value of neurobiological research and biomedical innovation. Yet, they seemed to argue that *any* research that can produce prevention and effective interventions is very timely needed, so long as it helps to respond to the needs of their ill relatives. On the contrary, harm can derive from neglecting such needs, and from *not* considering the personal and social circumstances in which technological innovation takes place. Carers were angry at their present situation. They hoped for and demanded an improvement in their relatives' treatment, but also feared that technological innovation might worsen their relatives' situation.

Carers' expertise consists precisely in holding this knowledge—they know their cared for's needs—by virtue of their position and of the caring values they cultivate. In the words of Virginia Held, "the central focus of the ethics of care is on the compelling moral salience of attending to and meeting the needs of particular others for whom we take responsibility."[34] Adopting such an approach poses a challenge to ethics scholarship. Should we frame the ethics discourse by taking into account carers' suggestions? Let us consider psychosis prevention. According to carers, prevention (and prediction) of psychosis are strongly needed. Carers seem to suggest that the real moral challenge of psychosis prevention does not consist in

[33] Tronto, *op. cit.*, 105.
[34] Held, *op. cit.*, 10.

whether or not this might be beneficial.[35] Rather, psychosis prevention presents a different moral dilemma. Effective prevention and prediction are needed, but *at what cost*? Are the risks or over-diagnosis, medicalisation, and the burden on young people acceptable? How do we minimise such risks?

Care can be understood as practice and as value.[36] This study suggests that, while promoting treatment in the community, we should take into account the actors who take responsibility for such caring practices and the values they hold. Again, the issue of confidentiality can be taken as a good example of this dynamic. Confidentiality is perceived as a conflictual ethical issue because it does pose a moral conflict: respect for patient autonomy conflicts with carers' need to be involved in research and treatment decisions.[37] An uncritical focus on autonomy might not provide appropriate avenues to solve this conflict, especially in mental health care. Even when they retain their capacity, carers' ill relatives are not aloof from their carers as their actions are embedded within a caring relationship. Not recognising this fact means, at least, disrupting the caring relationship. Care ethics poses a serious critique to liberal individualism by promoting a relational theory of the person.[38] A relational interpretation of autonomy might help to solve the issue of confidentiality in mental health.

Lastly, this study suggests that carers' demands are not only ethical but also *political*. Carers demand a substantial restructuring of how society deals with mental illness in recognition of the value of caring. This principle must accompany technological innovation in mental health. As Joan Tronto has claimed, carers' anger emerges from their struggle to separate their own needs from the needs of those they care for, where resources are insufficient.[39] Carers' rage, their hopes and fears might help us to translate technological innovation into psychiatry so that those who suffer from psychosis might effectively benefit from it.

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[35] Appelbaum, Paul S., 'Ethical Challenges in the Primary Prevention of Schizophrenia', *Schizophrenia Bulletin* 41 (4) (2015): 773-775.
[36] Held, *op. cit.*, 29.
[37] Szmukler, George I. and Bloch, Sidney, 'Family involvement in the care of people with psychoses. An ethical argument', *British Journal of Psychiatry* 171 (5) (1997): 401-405.
[38] Held, *op. cit.*, 13.
[39] Tronto, *op. cit.*, 143.

4.6 Conclusions

Technological innovation has the potential to transform the care of those who suffer from psychotic illness. Novel interventions, effective medications, and accurate prevention tools are likely to result from an increased understanding of the neurobiology of psychosis, fuelled by the converge of neuroscience, genomics, and data science.[40] The findings of this study suggest that carers of those who suffer from psychosis can provide an interesting outlook on the moral challenges arising from this endeavour. This outlook is narratively rich and epistemically valuable. Given carers' vital role in supporting treatment in the community, their narratives are an essential source of knowledge for bioethics. This study further suggests that carers' conceptualisations of ethical challenges may not be necessarily focused on the traditional issues of capacity, coercion, and management of neurobiological information. This does not mean that such issues do not deserve the attention that bioethicists usually reserve them. Rather, I argue that bioethics could greatly benefit from acknowledging carers' expertise in framing the ethics debate.

According to mental health carers, research and care *ought to* move forward. Because now they are not moving forward. Because their relatives' poor quality of life requires that research and care move forward. More precisely, carers *demand* that research and care move forward. A clearer understanding of the neurobiology of psychosis could help psychiatric research and mental health care to move forward. It could help to ameliorate the lives of those who suffer from psychosis, mitigate carers' frustration and support them in their caring role. Yet, it could also result in over-diagnosis, medicalisation, and excessive burden on (young) patients and service users. According to the participants in this study, which way it goes will depend on whether the needs of those who suffer from psychosis are appropriately met. In this sense, as I have argued in this article, mental health carers' outlook on sensitive bioethical issues can be properly understood only by referring to an ethics of care. Carers' vital role precisely consists in helping to make sure that their relatives' needs are assessed, understood, and met, while we transform how our societies deal with severe mental illness.

[40] Thompson and Broome (eds.), *op. cit.*

4.7 Data availability

The data supporting the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants. The data may be made available by the corresponding author upon a reasonable request from a bona fide researcher in order to validate the reliability of data analysis.

5. ARTICLE FOUR | The risks of risk. Regulating the use of machine learning for psychosis prediction

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Summary

This article contributes to answering my thesis research question by investigating some of the legal challenges presented by technological convergence in psychiatry. Developments in neuroscience and genomics result in an increased understanding of the neurobiology of psychosis and in an increased capacity to gather neurobiological information. This article investigates the legal challenges of using that information with machine-learning applications. More precisely, the article investigates the legal challenges of using machine learning for psychosis prediction. Clinical prediction via machine learning is currently one of the most important avenues for the clinical use of neurobiological information, as well as one of the

most discussed loci for technological convergence in psychiatry. In order to ensure that technological convergence may truly benefit people who suffer from psychosis, it is essential to assess how machine learning will—and should—be regulated in psychiatry. The article focuses on the jurisdiction of England and Wales. It argues that the use of machine learning for psychosis prediction is already to some extent regulated by existing regulation: clinical research and data protection regulation and mental health legislation. The article explores the notions of 'risk' and 'harm' and provides suggestions as to how machine learning should be regulated—and used—in psychiatric research and mental health care.

5.1 Abstract

Recent advances in Machine Learning (ML) have the potential to revolutionise psychosis prediction and psychiatric assessment. This article has two objectives. First, it clarifies which aspects of English law are relevant in order to regulate the use of ML in clinical research on psychosis prediction. It is argued that its lawful implementation will depend upon the legal requirements regarding the balance between potential harms and benefits, particularly with reference to: (i) any additional risks introduced by the use of ML for data analysis and outcome prediction; and (ii) the inclusion of vulnerable research populations such as minors or incapacitated adults. Second, this article investigates how clinical prediction via ML might affect the practice of risk assessment under mental health legislation, with reference to English law. It is argued that there is a potential for virtuous applications of clinical prediction in psychiatry. However, reaffirming the distinction between psychosis risk and risk of harm is paramount. Establishing psychosis risk and assessing a person's risk of harm are discrete practices, and so should remain when using artificial intelligence for psychiatric assessment. Evaluating whether clinical prediction via ML might benefit individuals with psychosis will depend on which risk we try to assess and on what we try to predict, whether this is psychosis transition, a psychotic relapse, self-harm and suicidality, or harm to others.

5.2 Introduction

David Reynolds was diagnosed with schizophrenia in 1998 at the age of 29. On 16 March 2005, Mr Reynolds contacted his care coordinator at a local National Health Service (NHS) mental health team: he was hearing voices ordering him to kill himself. The care coordinator told him that he could have a crisis bed in a local intensive support unit. A clinical assessment was conducted and he told the psychiatrist that he did not want to kill himself. He had no history of self-harm or attempted suicide. Mr Reynolds was assessed to be a low suicide risk and was admitted as a voluntary inpatient. At around 10.30pm he broke a window in his room and fell from the sixth floor to his death. In March 2012, the European Court of Human Rights (ECtHR) ruled that there had been a violation of Article 2(1) of the European Convention of Human Rights (ECHR), which provides, "[e]veryone's right to life shall be protected by law."[1] Did Mr Reynolds want to kill himself? What if we had reliable measures of suicide risk that do not rely on self-reporting? What would happen if we could predict whether someone will develop a psychotic episode before he or she eventually slips into full-blown psychosis?

The advent of countless forms of Artificial Intelligence (AI) is transforming the way in which we design and deliver health care.[2] Legislation, however, evolves slower than technology. While the hype is great, numerous are the questions: how will technology transform the way in which we diagnose mental illness? How do we regulate the myriad of AI applications that are being developed in mental health care? Most importantly, how can AI applications be developed to be 'forces for good',[3] and to not become the biased actors of injustice and State control that Cathy O'Neil has eloquently described as 'weapons of math destruction'?[4]

The present article provides a contribution to this emerging field of ethical and legal theory by trying to answer a narrower question: what legal challenges

[1] *Reynolds v. The United Kingdom* (2012) 55 EHRR 35.
[2] Alpaydin, Ethem, *Machine learning: the new AI* (Cambridge, Massachusetts: The MIT Press, 2016); Dadich, Scott, 'Barack Obama, neural nets, self-driving cars, and the future of the world', https://www.wired.com/2016/10/president-obama-mit-joi-ito-interview/, last accessed 20 July 2019; Shatte, Hutchinson, and Teague, *op. cit.*
[3] Taddeo, Mariarosaria and Floridi, Luciano, 'How AI can be a force for good', *Science* 361 (6404) (2018): 751-752.
[4] O'Neill, Cathy, *Weapons of Math Destruction. How Big Data Increases Inequality and Threatens Democracy* (Penguin Books, 2016).

arise from the use of Machine Learning (ML)—a specific form of AI—in the context of psychosis prediction? More specifically, the present contribution has two objectives. First, it wishes to clarify which aspects of English law are relevant in order to regulate the use of ML in *clinical research* on psychosis prediction. Second, it wishes to investigate how ML might affect the practice of *psychiatric assessment* in the context of psychosis. Technological innovation opens up the possibility to identify psychosis risk, predict psychosis transition or relapse, and foresee harm to self or others. This article explores the notions of 'psychosis risk' and 'risk of harm'. It investigates how these notions relate to the issue of diagnostic uncertainty in psychiatric assessment and the implications of such concepts for legal theory. It is argued that there is a potential for virtuous applications of AI-mediated prediction in mental health. However, maximising this potential will require a careful evaluation of how we interpret different notions of 'risk'. This article refers to the jurisdiction of England and Wales. However, the reflections presented here may be relevant to other jurisdictions.

5.3 Machine learning and psychosis prediction(s)

"[P]sychiatry is not an exact science."[5] Nonetheless, technology is reshaping the way in which we understand, diagnose, and treat psychotic illness. This article does not address the question of whether it is ethically acceptable to use ML to predict psychotic illness. Rather, it provides some clarifications on how to regulate a number of recent advances in medical technology in the context of psychosis. It follows a simple principle: in order to understand how to regulate the use of medical technologies, it is essential to understand how such technologies are used, and how they are likely to be used in the near future. According to Jiang et al., AI systems are being designed in health care with three aims: (i) to reduce diagnostic uncertainty by helping clinicians to classify individuals in different populations; (ii) to support identification of at-risk status for specific conditions, and (iii) to help to predict health outcomes, thus supporting clinical prevention.[6] Classification, risk

[5] *Regina v. Ashworth Hospital Authority* [2005] UKHL 20, [2005] 2 AC 278, at para 31.
[6] Jiang, Fei et al., 'Artificial intelligence in healthcare: past, present and future', *Stroke and Vascular Neurology* 2 (4) (2017): 230-243.

identification, and prediction are the ways in which AI—mostly ML applications—is currently used in the context of psychosis.

Let us unfold this further. First, what is ML? The term ML identifies a number of techniques used to analyse data and to make outcome predictions. The Information Commissioner's Office (ICO) has borrowed a definition from iQ, Intel's tech culture magazine, which defines ML as the "set of techniques and tools that allow computers to 'think' by creating mathematical algorithms based on accumulated data."[7] ML is a sub-field of narrow AI—that is, AI which is designed for a specific application, and not to fully resemble human intelligence.[8] It is used for data analysis, whereby software is trained from a dataset to classify the data, identify patterns, and make predictions. As Alpaydin writes, "it is easy to collect data, and now the idea is to learn the algorithms for these [applications] automatically from the data, replacing programmers with learning programmes. This is the niche of machine learning".[9] ML algorithms can be described as *supervised*, *unsupervised*, or *semi-supervised* depending on the degree of pre-classification of the datasets used to train and develop the algorithm.[10]

Second, how is ML currently used in mental health? Shatte et al. have recently provided a very useful scoping review.[11] The authors identify four domains of application: (i) detection and diagnosis; (ii) prognosis, treatment and support; (iii) public health; and (iv) research and clinical administration. The vast majority of studies reviewed falls within the first two domains. The first domain includes studies that attempt to *classify* clinical groups and *identify risk* status for mental health conditions, among which are psychosis and schizophrenia. The second domain includes attempts to *predict* clinical outcomes again for a number of conditions including psychosis and schizophrenia. Interestingly, the second domain also includes studies whose purpose was to identify suicidal ideation and to predict self-harm and suicide. Indeed, self-harm and suicidal ideation do not represent discrete diagnostic categories. Rather, they are occurrences which characterise

[7] See Information Commissioner's Office, *Big data, artificial intelligence, machine learning, and data protection*, *op. cit.*, 7.
[8] Turner, *Robot Rules. Regulating Artificial Intelligence*, *op. cit.*
[9] Alpaydin, *op. cit.*, X.
[10] Shatte, Hutchinson, and Teague, *op. cit.*
[11] Ibid.

mental disorders across the diagnostic spectrum,[12] and which have been reported also in the early stages of psychosis.[13]

Third, which types of data sources are fed to ML algorithms to accomplish these tasks? Data sources used to develop ML algorithms vary considerably. They include—but are not limited to—neuroimaging data, clinical assessment and clinical record data, digital health data collected via wearables and digital phenotyping,[14] and speech data. Shatte et al. highlight that "the majority of studies investigating the detection and diagnosis of mental health conditions used neuroimaging data with supervised classification techniques."[15] Neuroimaging has traditionally been used to investigate the neural correlates of psychosis and schizophrenia.[16] In the past decades, early intervention services have started promoting psychosis prevention by targeting people at clinical High-Risk (HR) of psychosis.[17] Neuroimaging data are currently used to investigate the psychosis HR state, to support the classification of clinical groups,[18] and to predict psychosis transition in HR individuals.[19] For instance, Koutsouleris et al. were recently able to predict transition outcomes in 80% of individuals using MRI data.[20] Clinical assessment and clinical record data are being used to predict psychosis transition in HR individuals,[21] and to identify suicidal ideation and predict suicide attempts.[22]

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[12] Harris, E. Clare and Barraclough, Brian, 'Suicide as an outcome for mental disorders. A meta-analysis', *British Journal of Psychiatry* 170 (3) (1997): 205-228.
[13] Xu, Ziyan et al., 'Pathways between stigma and suicidal ideation among people at risk of psychosis', *Schizophrenia Research* 172 (1-3) (2016): 184-188.
[14] Jain, Sachin H. et al., 'The digital phenotype', *Nature Biotechnology* 33 (5) (2015): 462-463.
[15] Shatte, Hutchinson, and Teague, *op. cit.*, 1434.
[16] 'Neuroimaging' is used here as an umbrella term to indicate a number of techniques used to study brain structures (structural Magnetic Resonance Imaging, or MRI), brain functions (functional Magnetic Resonance Imaging, or fMRI), or neurotransmitter dysfunction and other molecular processes (various imaging techniques such as Single Photon Emission Tomography, or SPET, and Positron Emission Tomography, or PET). For an interesting overview of neuroimaging techniques used in psychosis studies, see McGuire et al., *op. cit.*
[17] Fusar-Poli et al., 'The psychosis high-risk state: A comprehensive state-of-the-art review', *op. cit.*
[18] Kempton, Matthew J. and McGuire, Philip, 'How can neuroimaging facilitate the diagnosis and stratification of patients with psychosis?', *European Neuropsychopharmacology* 25 (5) (2015): 725-732; Valli et al., *op. cit.*
[19] Gifford et al., *op. cit.*
[20] Koutsouleris et al., *op. cit.*
[21] Mechelli, Andrea et al., 'Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis', *Schizophrenia Research* 184 (2017): 32-38.
[22] Fernandes, Andrea C. et al., 'Identifying Suicide Ideation and Suicidal Attempts in a Psychiatric Clinical Research Database using Natural Language Processing', *Scientific Reports* 8 (1) (2018): 7426; Walsh, Colin G., Ribeiro, Jessica D., and Franklin, Joseph C., 'Predicting Risk of Suicide

The use of digital health data in digital phenotyping holds promise to revolutionise prediction of psychosis *relapse* in individuals with schizophrenia.[23] In addition, also speech data are being used to predict psychosis transition in HR individuals[24] and to identify suicidal ideation and suicide attempts.[25]

What applications are relevant for the purpose of our analysis? In other words, what is relevant when we discuss ML-mediated psychosis prediction? We can identify three main areas of interest: (i) the use of ML with different datasets to enhance the identification of psychosis *risk* and the prediction of psychosis *transition* in HR individuals; (ii) the use of ML for prediction of psychosis *relapse* in individuals who suffer from a psychotic disorder, including schizophrenia; and (iii) the use of ML for the identification of risk of *harm*, as well as for prediction of self-harm and suicide in the context of psychosis. If the relevance of the first two areas stems from the importance of diagnostic and prognostic prediction in the context of psychosis, the importance of the third area originates from the fact that mental health legislation—at least in England and Wales—places great emphasis on the assessment of risks associated with mental disorders.[26] Legal scholarship has traditionally targeted the use of neuro-technology for the evaluation of criminal responsibility or for establishing the presence of a neurological condition.[27] Little attention has been dedicated to the use of AI for psychosis prediction and civil admission of the mentally ill. In this paper, I argue that legal challenges emerge within two domains: the conduct of clinical research and the practice of psychiatric assessment.

Attempts Over Time Through Machine Learning', *Clinical Psychological Science* 5 (3) (2017): 457-469.

[23] Barnett et al., *op. cit.*; Torous, John et al., 'Towards Digital Phenotyping for Relapse Prediction in Schizophrenia', *Early Intervention in Psychiatry* 12 (2018): 40.

[24] Bedi, Gillinder et al., 'Automated analysis of free speech predicts psychosis onset in high-risk youths', *npj Schizophrenia* 1 (2015): 15030; Corcoran, Cheryl M. et al., 'Prediction of psychosis across protocols and risk cohorts using automated language analysis', *World Psychiatry* 17 (1) (2018): 67-75; Rezaii, Neguine, Walker, Elaine, and Wolff, Phillip, 'A machine learning approach to predicting psychosis using semantic density and latent content analysis', *npj Schizophrenia* 5 (1) (2019): 9.

[25] Fernandes et al., *op. cit.*

[26] Bartlett and Sandland, *op. cit.*; Fanning, John, 'Continuities of Risk in the Era of the Mental Capacity Act', *Medical Law Review* 24 (3) (2016): 415-433; Glover-Thomas, *op. cit.*

[27] Meynen, Gerben, 'A neurolaw perspective on psychiatric assessments of criminal responsibility: decision-making, mental disorder, and the brain', *International Journal of Law and Psychiatry* 36 (2) (2013): 93-99; Spranger, Tade Matthias (ed.), *International Neurolaw. A Comparative Analysis* (Berlin, Heidelberg: Springer, 2012).

5.4 Regulating clinical research

In their scoping review of ML applications in mental health, Shatte et al. state that: "[v]ery little research was found that demonstrated the use of ML techniques in real-world settings, suggesting that further research is required to test clinical utility."[28] Psychosis prediction via ML has yet to become a clinical reality. In addition, as Shatte et al. have noted, even though the majority of ML studies investigating detection and diagnosis have until now used neuroimaging data, it seems problematic to foresee widespread access to imaging services for diagnostic purposes.[29] Thus, we might argue that the implementation of ML which uses other data sources seems, to date, more likely. Nonetheless, cases in which ML is used in psychiatric practice seem to be still rare. Before this translation happens, ML will make its way into the realm of clinical research. For this reason, I believe it is important to investigate how research ethics restrictions might influence later downstream applications. The debate on how to regulate AI in clinical research is still in its infancy. Efforts to regulate AI with statutory instruments are currently underway at a national and international level.[30] As AI makes its way into the practice of psychiatry, it falls within the scope of medical research regulation.[31] Therefore, the lawful implementation of ML in medical research will depend upon jurisdictional research governance frameworks. This article refers to the regulatory framework in England and Wales.

Balancing the duty to generate new knowledge with the interests of research participants has been at the core of the efforts to regulate medical research since the WMA Declaration of Helsinki.[32] This is particularly relevant when those who are targeted by research programmes are in a condition that may increase their

[28] Shatte, Hutchinson, and Teague, *op. cit.*, 1438.
[29] Ibid., 1434.
[30] Turner, *Robot Rules. Regulating Artificial Intelligence*, *op. cit.*
[31] See Turner, Jacob, 'Building a Regulator', *Robot Rules. Regulating Artificial Intelligence* (Palgrave Macmillan, 2018), 207-262.
[32] As expressed in Article 8 of the Declaration, "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects", World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects [1964], VII revision 2013.

vulnerability: young people, clinical populations, and people with enduring and severe mental illness. In order to ensure the lawful conduct of ML research in the context of psychosis prediction, I argue that two areas of regulation are of particular relevance: (1) protection of research participants, and (2) privacy and data protection.

5.4.1 Risks, benefits, and protection of research participants

Protection of participants in clinical research is generally intended as protection from potential harms that may be disproportionate to the benefits of the research. Informed consent is meant to ensure that participants are aware of the objectives of the research, and of potential harms and benefits. Within the UK regulatory framework, protection of research participants and informed consent procedures depend on two elements: (i) *who* are the research subjects—with reference to the legal age of competence and to the capacity to consent—and, (ii) what *type* of research is performed—whether this is general healthcare research or a clinical trial.

In England and Wales, Research Ethics Committees (RECs) are responsible for evaluating the risk-benefit ratio of research studies.[33] It is important to highlight one principle. When RECs evaluate the risk-benefit ratio of a research study—especially in the case of vulnerable populations—such evaluation is performed with reference to research *procedures*; in other words, to what will happen to research subjects as a result of their participation. This is evident in the discussion around the 'minimal risk' threshold in research with children, which is often interpreted as the risk that is "ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests."[34] The use of ML constitutes in itself a research procedure. However, ML is a set of techniques for data *analysis*. Therefore, the assessment of risks and benefits must take into consideration whether any additional risks to participants derive directly from the

[33] Where there is no investigation of medical products or devices—which in England and Wales is regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA)—RECs are the *only* agencies that evaluate the risk-benefit ratio of a research study.

[34] This wording is taken from the US Federal Regulations as reported in Kopelman, Loretta M., 'Minimal risk as an international ethical standard in research', *Journal of Medicine and Philosophy* 29 (3) (2004): 351-378: 360. See also Shah, Seema et al., 'How do institutional review boards apply the federal risk and benefit standards for pediatric research?', *JAMA* 291 (4) (2004): 476-482.

use of ML for data analysis and outcome prediction, in addition to the risks posed by data acquisition procedures. Let us try to unfold what the implications of this principle might be in the jurisdiction of England and Wales.

First, let us consider the case of adults who retain capacity to consent. The case of David Reynolds, which I introduced earlier, may provide a good example of the legal challenges of implementing ML-mediated prediction of harm in individuals with psychosis. David Reynolds was an adult and retained his capacity to consent to hospital admission for medical treatment—consent which he, in fact, had given.[35] In principle, there appear to be no reasons why he should not be allowed to consent to (at least) therapeutic medical research. However, few would deny that Mr Reynolds was in a vulnerable condition: he was actively psychotic, had ongoing suicidal ideation, and was seeking help. Should we consider including someone like Mr Reynolds in a research study in order to track his behaviour and establish his risk to commit a suicide attempt? From an ethical point of view, we may recognise the presence of two moral duties: the duty to protect the subject's life,[36] and the duty to conduct research with vulnerable individuals in order to improve suicide prevention. At the same time, the primary aim of clinical research regulation is to protect participants from disproportionate risks and burdens. How do we minimise *risk,* when the aim of a research programme is to investigate someone's risk (likelihood) to commit self-harm, or even a suicide attempt?

It can be argued that the use of wearables, digital phenotyping, or the collection of speech data poses minimal risks in terms of data acquisition. As Martinez-Martin et al. argue, "[t]he collection of digital data is ostensibly of relatively low risk, as it consists of the same activities an individual would otherwise engage in."[37] The same could be said with reference to the use of data collected via clinical assessment or clinical records. It is less clear whether data acquisition via neuroimaging poses significant risks in the context of psychosis, though it has been argued that the use of neuroimaging with vulnerable populations,

[35] *Reynolds v. The United Kingdom* (2012) 55 EHRR 35.
[36] As recognised also by the ECtHR in *Reynolds v. The United Kingdom* (2012) 55 EHRR 35.
[37] Martinez-Martin, Nicole et al., 'Data mining for health: staking out the ethical territory of digital phenotyping', *npj Digital Medicine* 1 (2018): 68: 3.

such as children, can be classified as minimal risk.[38] Does the use of ML for data analysis pose any *additional* risks? Recent literature has highlighted two relevant sets of risks related to the use of ML in health care: risks to privacy and data protection, and the risk of algorithmic bias.[39] I shall briefly address the issue of data protection later in this article. Here, to answer our original question, I argue that in order to minimise risk in ML research on self-harm in psychosis, researchers should: (1) employ low-risk data acquisition techniques; (2) ensure that appropriate data protection protocols are in place; and (3) minimise algorithmic bias in ML design. Further, I argue that such principles should not be confined to the ML research on self-harm and suicidality. They may be applied to ML research which aims to identify psychosis risk or to predict psychosis transition or relapse in adults who retain capacity to consent.

Second, let us consider the case of minors and children. Early intervention services in England and Wales target people aged 14 to 65.[40] It is thus a possibility that minors are asked to participate in ML research, particularly with reference to prediction of psychosis *transition* in HR individuals, or prediction of self-harm. English law has established clear guiding principles for the conduct of research with minors.[41] In the case of healthcare research, *Gillick* competent minors—and legal representatives of other minors— may consent to research that produces no direct benefits if this is not against the child's best interests.[42] Unless ML procedures are shown to be against a child's best interest, the consent of Gillick competent minors (and of legal representatives of other minors) should be sufficient. The situation is more complicated with regard to clinical trials. Clinical trials conducted in England and Wales fall under the Medicines for Human Use (Clinical Trials) Regulations

[38] Holland, Scott K. et al., 'Data on the safety of repeated MRI in healthy children', *NeuroImage: Clinical* 4 (2014): 526-530.
[39] Mittelstadt, Brent D. et al., 'The ethics of algorithms: Mapping the debate', *Big Data & Society* 3 (2) (2016): 1-21; Vayena, Effy, Blasimme, Alessandro, and Cohen, I. Glenn, 'Machine learning in medicine: Addressing ethical challenges', *PLoS Med* 15 (11) (2018): e1002689. See also 'Accuracy', in Information Commissioner's Office, *Big data, artificial intelligence, machine learning, and data protection*, *op. cit.*, 43-45.
[40] See NHS England, *Implementing the Early Intervention in Psychosis Access and Waiting Time Standard: Guidance* (2016).
[41] See Brazier, Margaret and Cave, Emma, 'Young people in medical research programmes', *Medicine, patients and the law* [VI edition] (Manchester: Manchester University Press, 2016), 485-489.
[42] See ibid.

2004.[43] However, this regulation may soon be replaced by the Clinical Trials Regulation EU No 536/2014.[44] The new general rule will be as follows: the informed consent of the minor's legal representative must be obtained;[45] "the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors";[46] a *direct benefit* for the minor can be expected, *or* some benefit for the *population* represented can be expected *and* the trial only poses *minimal risk*.[47]

We can argue that clinical trials that use ML to enhance the identification of psychosis risk or to ameliorate prediction of psychosis transition *should*—in theory—be able to offer the prospect of a *population benefit*; their rationale being precisely to ameliorate diagnostic procedures and prediction in the context of psychosis. Should they be classified as minimal risk? Let us look at data acquisition. Again, there is evidence to believe that neuroimaging poses minimal risks to children;[48] the same is valid for data collection via clinical assessment, clinical records, and digital health applications. What about ML data analysis procedures? As I argued above, it will be important to assess whether the use of ML for data analysis might pose any *additional* risks to the minors involved in the clinical trial. In England and Wales, it will be RECs' responsibility to establish whether ML procedures expose minors to risks that are more than minimal, again especially with regard to data protection and the risk of algorithmic bias.

Third, let us consider the case of adults who lack mental capacity. It should not be assumed that individuals who suffer from psychosis lack the capacity to

[43] According to the 2004 Regulations, the age of consent is set at 16 years; informed consent by a parent or a legal representative is required for minors (Part 4, para 4); and some direct benefit for the group of patients involved in the trial must be obtained (Part 4, para 10).
[44] The new Regulation will be applied after the development of a fully functional EU clinical trials portal and database, which is currently estimated to occur in 2020. At the time of writing, it is difficult to predict what will be the consequences of Brexit on the application of the Regulation in the United Kingdom. Also, note that the 'direct benefit for the group of patients involved' criterion established by the 2004 English Regulations is more restrictive than the '*population* benefit' required under the new EU Regulation.
[45] Article 32 (1) (a), Clinical Trials Regulation EU No 536/2014.
[46] Ibid., Article 32 (1) (f).
[47] Ibid., Article 32 (1) (g).
[48] Holland et al., *op. cit.*

consent to research.[49] At the same time, it must be acknowledged that a clinical history of severe mental illness might affect capacity.[50] Therefore, it is not unlikely that ML research on prediction of psychosis relapse or self-harm in individuals with schizophrenia might involve people who lack capacity to consent. Here, English law is more complicated than in the case of minors. Healthcare research with incapacitated subjects is governed in England and Wales by the Mental Capacity Act 2005 (MCA). Under the MCA, the research must have the potential to *benefit* the subject without imposing a disproportionate burden, *or* be intended to provide knowledge about the condition from which the incapacitated subject is affected.[51] In the latter case, the *risk* must be *negligible*,[52] and research procedures should not be *unduly* invasive or restrictive.[53] With regard to the criterion of 'benefit' to the subject, the MCA Code of Practice specifies that potential benefits include "developing more effective ways of treating a person or managing their condition" or "reducing the risk of the person being harmed".[54] In theory, it seems that ML research that aims to improve prediction of psychotic relapse and self-harm could satisfy this requirement. With regard to the criterion of 'negligible risk', we can refer to the reflections presented above regarding the minimal risk threshold in minors.

In the case of clinical trials, the new EU Clinical Trials Regulation will establish the same risk-benefit criteria discussed above for minors.[55] However, until the new Regulation becomes applicable, clinical trials with incapacitated subjects in England and Wales will fall under the Medicines for Human Use (Clinical Trials) Regulations 2004. Under these Regulations, informed consent must be obtained from the subject's legal representative,[56] and there must be 'grounds' to think that the trial will produce *direct benefit* to the individual, or *no risk at all*.[57] RECs will

[49] Spencer, Benjamin W. J. et al., 'Unwell in hospital but not incapable: cross-sectional study on the dissociation of decision-making capacity for treatment and research in in-patients with schizophrenia and related psychoses', *British Journal of Psychiatry* 213 (2) (2018): 484-489.
[50] Appelbaum, 'Decisional Capacity of Patients With Schizophrenia to Consent to Research: Taking Stock', *op. cit.*
[51] Mental Capacity Act 2005, section 31(5).
[52] Ibid., section 31(6)(a).
[53] Ibid., section 31(6)(b)(ii).
[54] Department for Constitutional Affairs, *op. cit.*, chap. 11.14, 207.
[55] See Article 31, Clinical Trials Regulation EU No 536/2014.
[56] Medicines for Human Use (Clinical Trials) Regulations 2004, schedule 1, part 5.
[57] Ibid., condition (1)9.

have to consider whether a prospect of direct benefit can be established from ML-mediated prediction of psychosis relapse or self-harm. At the same time, it might be more difficult to demonstrate that a clinical trial poses 'no risk at all' for incapacitated participants, considering the risks to data protection and the risk of algorithmic bias mentioned above.

To summarise: what additional risks may result from the use of ML for data analysis and outcome prediction? In relation to which populations? How should researchers and RECs try to minimise these risks and maximise the benefits of ML-mediated prediction in the context of psychosis? Answering these questions could ensure that research studies prioritise the rights and interest of participants over the duty to produce new knowledge, as established by the WMA Declaration of Helsinki.

5.4.2 Privacy and data protection

The development of AI in healthcare poses significant challenges to privacy and data protection.[58] It is beyond the scope of this paper to provide a comprehensive account of these challenges. However, it is important to mention some recent developments in the European data protection framework. The General Data Protection Regulation 2016/679 (GDPR),[59] which was incorporated into English law with the Data Protection Act 2018, can be considered the first European regulation to deal explicitly with data processing by means of AI. The GDPR is relevant to psychosis prediction for two reasons. First, it sets out the legal framework for processing health-related data. Second, it establishes some important limitations to *automated* data processing.

Under GDPR, the level of data protection depends upon which type of data is being processed. At Article 4, the GDPR distinguishes among: (i) genetic data, (ii) biometric data, and (iii) data concerning health. Neuroimaging data could be classified as either biometric or as data concerning health, though it seems likely

[58] Information Commissioner's Office, *Big data, artificial intelligence, machine learning, and data protection*, *op. cit.*; Vayena, Blasimme, and Cohen, *op. cit.*

[59] Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

that data obtained for the purpose of *clinical* prediction shall be classified as data concerning health.[60] How will clinical assessment data and behavioural data collected via wearables and digital phenotyping be classified? Article 4 specifies that, "'data concerning health' means personal data related to the physical and mental health of a natural person, […] which reveal information about his or her health status".[61] Therefore, we can assume that clinical assessment and behavioural data collected for clinical prediction constitute data concerning health. Article 9 clarifies that genetic data, biometric data, and data concerning health constitute 'special-category personal data', and are thus subject to specific rules for processing. Processing of special-category personal data is permitted, among other conditions, in the case of: (a) explicit consent of the data subject, (c) to protect the *vital interest* of the data subject or another natural person, where the data subject is not able to give consent, (g) for reasons of 'substantial public interest', (h) for the purposes of 'preventive medicine' and 'medical diagnosis', and for (j) research purposes.[62]

Under Article 8(2) ECHR, the right to respect for private life is not absolute as exceptions are permitted, including "for the prevention of disorder or crime" and "for the protection of health or morals". The GDPR, however, establishes some important limitations to the use of automated decision-making in this regard. First, the data subject must be informed of the existence of automated decision making regardless of whether or not the data are collected from him or her.[63] Second, Article 22(1) recognises "the right not to be subject to a decision based *solely* on automated processing, including profiling, which produces legal effects [concerning the data subject]". Even though exceptions to this rule are possible, in the case of special-category personal data these exceptions are admissible only with the explicit consent of the data subject, *or* "for reasons of substantial public interest".[64]

Some considerations can thus be drawn on how ML will be used in the context of psychosis prediction. First, it appears that data collected for the purpose

[60] For instance, the UK Biobank GDPR notice classifies data collected, including neuroimaging data, as health-related data, see https://www.ukbiobank.ac.uk/gdpr/, last accessed 6 July 2019.
[61] Regulation (EU) 2016/679, Article 4(15).
[62] Ibid., Article 9(2).
[63] Ibid., Article 13(2)(f) and Article 14(2)(g).
[64] Ibid., Article 22(4).

of clinical prediction—be it prediction of psychosis transition, relapse, or harm—will be classified as 'special-category personal data' and be subject to specific rules for processing, both in research and in clinical contexts. Second, the data subject will retain the right to be informed of the existence of ML procedures, as these constitute automated processes. Third, and most importantly, it appears that the data subject will retain the right to object to decisions based *solely* on the outcomes of ML algorithmic applications. It might not be possible for clinicians, for instance, to delegate decisions following confirmation of risk status or outcome prediction to fully automated ML applications. Clinicians and public authorities will retain legal responsibility for the decisions they take concerning a data subject, following identification of risk status or outcome prediction via ML applications.

5.5 Psychiatric assessment and ML-mediated prediction

Even though ML applications are currently mostly confined to clinical research,[65] it is important to anticipate how they might shape mental health care in the near future. Many civil and common-law jurisdictions recognise *risk* criteria for compulsory admission or treatment of the mentally ill.[66] As we move towards clinical prediction in mental health, the use of AI will likely affect the practice of *psychiatric assessment* under mental health legislation. In the next pages, I investigate how ML might affect the practice of psychiatric assessment and determination of risk in the context of psychosis, with reference to English law.

The *logic of risk* is apparent under English law.[67] Compulsory hospital admission and treatment for the mentally ill is governed in England and Wales by the Mental Health Act 1983 (MHA).[68] Individuals who suffer from a mental disorder may be detained in hospital for assessment followed by treatment if, *inter alia*, this is "necessary for the health or safety of the patient or for the protection of other

[65] Shatte, Hutchinson, and Teague, *op. cit.*
[66] de Stefano and Ducci, *op. cit.*; Ryan, Christopher et al., 'Clinical decisions in psychiatry should not be based on risk assessment', *Australasian Psychiatry* 18 (5) (2010): 398-403.
[67] Fanning, *op. cit.*; Glover-Thomas, *op. cit.*
[68] As amended by the Mental Health Act 2007.

persons".[69] Risk assessment is particularly relevant at patient discharge. Under the MHA, individuals who have been detained under section 3, for example, may be subject to a community treatment order if this is necessary for "preventing risk of harm to the patient's health or safety"[70] or for "protecting other persons."[71] As elegantly phrased by the ECtHR, mental health legislation deals with the "unpredictability of human conduct".[72] English law recognises *risk of harm* to self or others as the main criterion for civil detention or compulsory treatment of the mentally ill. The discriminatory nature of such practice is being contended in light of the United Nations Convention on the Rights of Persons with Disabilities.[73] Researchers are calling for a removal of risk criteria from mental health legislation.[74] This article does not address the issue of whether risk criteria are discriminatory. To date, such criteria remain part of our statutes. Rather, this article investigates how prediction via AI might affect our ability to manage the 'unpredictability of human conduct' in people who suffer from psychosis, within the context of current mental health law.

5.5.1 On risk

Until now, we have discussed the use of ML around three areas: (i) the identification of psychosis risk and the prediction of psychosis *transition* in HR individuals; (ii) the prediction of psychosis *relapse* in individuals who suffer from a psychotic disorder; and (iii) the prediction of self-harm and suicidality in the context of psychosis. As we have seen, Shatte et al. significantly include prediction of harm in their scoping review of ML applications in mental health.[75] Some nuanced distinctions are necessary. The field of clinical prediction and the practice of risk assessment under mental health law have something in common. This is the concept

[69] Mental Health Act 1983, Part II, section 3(2)(c).
[70] Mental Health Act 1983, section 17B(2)(b).
[71] Mental Health Act 1983, section 17B(2)(c).
[72] *Osman v. United Kingdom* (2000) 29 EHRR 245 at para 116.
[73] Szmukler, George, *Men in White Coats. Treatment Under Coercion* (Oxford: Oxford University Press, 2017).
[74] See also the recent Report of the Special Rapporteur on the rights of persons with disabilities A/HRC/40/54, released by the United Nations General Assembly Human Rights Council on 11 January, 2019, available at https://undocs.org/A/HRC/40/54, last accessed 6 July 2019.
[75] Shatte, Hutchinson, and Teague, *op. cit.*

of *risk* and the attempt to predict future behaviour. Nonetheless, establishing psychosis risk and assessing a person's risk of harm are discrete practices, though they may occasionally overlap. Here, I argue that the notion of *psychosis risk* and the notion of *risk of harm* are different in nature.

Psychosis risk is a clinical notion. In the past twenty years, this notion has emerged to identify (young) individuals who have not yet experienced a first episode of psychosis, but whose behavioural deterioration has reached a threshold that warrants clinical attention. The concept of psychosis risk has been operationalised in several denominations, including the HR state.[76] Moreover, amid a rather heated debate,[77] the latest edition of the DSM-5 eventually included the 'attenuated psychosis syndrome', whose criteria strongly resemble the ones of the psychosis HR state.[78] As a clinical notion, the concept of psychosis risk represents someone's likelihood to transition to—that is, to develop—a psychotic episode. Linked to the notion of psychosis risk is the occurrence of further psychotic episodes after a period of remission, which is usually called *psychosis relapse*.[79]

Risk of harm is a broader, complex ethico-legal notion. It refers to the harm that may derive from a mental disorder. The MHA Code of Practice defines risk of harm as "risk of: suicide, self-harm, self-neglect […] jeopardising [one's] own health or safety accidentally, recklessly or unintentionally, or […] otherwise putting [one's] health or safety at risk".[80] In addition, according to the Code, risk of harm includes potential harm to other people.[81] While psychosis risk can be conceptualised as the risk to develop a certain mental state (or illness), risk of harm can be conceptualised as the risk that harmful *consequences* may occur because of (the presence of) a mental state. In other words, the concept of risk of harm represents someone's likelihood to cause harm to herself or to a third party.

Using ML to establish psychosis risk is *not* the same as using ML to establish risk of harm. Interestingly, the MHA does not define 'risk'.[82] As outlined

[76] Fusar-Poli et al., 'The psychosis high-risk state: A comprehensive state-of-the-art review', *op. cit.*
[77] Yung, Alison R. et al., 'Should a "Risk Syndrome for Psychosis" be included in the DSMV?', *Schizophrenia Research* 120 (1-3) (2010): 7-15.
[78] See American Psychiatric Association, *op. cit.*, s. II, 122.
[79] Emsley, Robin et al., 'The nature of relapse in schizophrenia', *BMC Psychiatry* 13 (2013): 50.
[80] Department of Health, *Mental Health Act 1983: Code of Practice*, *op. cit.*, 114.
[81] Ibid., 115.
[82] Fanning, *op. cit.*

above, the definition provided by the Code of Practice is sufficiently loose to include any risks to the health of a person. It could be argued that psychosis transition in HR individuals, or psychosis relapse in individuals who suffer from schizophrenia might indeed 'jeopardise their health'. This is particularly true in the context of psychiatric assessment under the MHA. However, would this be sufficient to establish the presence of 'risk of harm'? The extent to which psychosis risk and risk of harm may overlap depends on whether we can consider psychosis as harmful *per se*. Does psychosis risk constitute a risk of harm to self/others and therefore qualify as a basis for intervention? Even though there are good reasons to believe that intervening early in the clinical course of psychotic illness is beneficial, there are also good reasons to believe that psychosis and psychotic illness are not the same.[83] People who have psychotic experiences—especially auditory hallucinations—greatly outnumber the ones who develop a psychotic disorder.[84] Therefore, we cannot consider psychosis as harmful *per se*. As AI ameliorates our ability to predict a psychotic episode, using psychosis risk as a criterion to justify coercion—if coercion can ever be justified—without any indication that harmful behaviour is likely to occur, could potentially have the *paradoxical* effect of harming the individual while trying to prevent harm. Psychosis risk and risk of harm are discrete entities, and should remain so. This principle may be valid regardless of the tools used to predict psychosis—whether this is done via clinical interview or via ML. However, it will be important to reaffirm this principle when translating ML applications into psychiatric assessment, in order to minimise the risk of algorithmic bias.

5.5.2 On prediction, algorithms, and coercion

The use of ML in psychiatry opens up the possibility to predict certain events and clinical outcomes. However, what exactly are we predicting when we use ML in

[83] Read and Dillon (eds.), *op. cit.*

[84] See for instance Bentall, Richard P., 'Understanding psychotic symptoms. Cognitive and integrative models', in John Read and Jacqui Dillon (eds.), *Models of Madness. Psychological, Social and Biological Approaches to Psychosis* [2nd edition] (London & New York: Routledge, 2013), 220-237.

the context of psychosis? Let us focus on four possible scenarios: (i) psychosis transition; (ii) psychosis relapse; (iii) self-harm and suicide; and (iv) harm to others.

First, predicting *psychosis transition* means that we are predicting that (young) high-risk individuals, who have never had psychosis, will develop a first psychotic episode.[85] It has long been established that individuals who experience a first psychotic episode should be offered participation in youth-friendly, community-based early intervention services.[86] In this case, coercion would most likely *generate harm*, not prevent it.

Second, predicting *psychosis relapse* means that we are predicting that individuals who already suffer from a psychotic disorder including schizophrenia will relapse into psychosis, with potentially harmful consequences for their health. Digital phenotyping is particularly promising in this regard.[87] Prediction of psychosis relapse could help to improve prognosis of severe mental illness. There is little doubt that reducing diagnostic uncertainty in psychiatry could produce clinical benefits. Yet, the issue of coercion remains unsolved. The case of *Winterwerp v. The Netherlands* has established that, in order for a deprivation of liberty to be lawful, "objective medical expertise" is needed to determine whether a person is of 'unsound mind', as well as to demonstrate the nature and degree of a "true mental disorder".[88] Relapse prediction could in fact support 'objective medical expertise' by providing a reliable estimate of who is likely to relapse into psychosis—and potentially, when. However, the issue of whether psychosis relapse may be *per se* harmful remains open. Risk of harm to self or others would still have to be established in order to authorise a deprivation of liberty.

Third, predicting *self-harm and suicide* means predicting harm to self or, in extreme cases, a suicide attempt.[89] In a recent article, Walsh et al. reported that they

[85] Koutsouleris et al., *op. cit.*; Rezaii, Walker, and Wolff, *op. cit.*

[86] Corsico, Paolo, Griffin-Doyle, Michelle, and Singh, Ilina, 'What constitutes 'good practice' in early intervention for psychosis? Analysis of clinical guidelines', *Child and Adolescent Mental Health* 23 (3) (2018): 185-193.

[87] Barnett et al., *op. cit.*; Torous et al., 'Towards Digital Phenotyping for Relapse Prediction in Schizophrenia', *op. cit.*

[88] *Winterwerp v. The Netherlands* (A/33) (1979-80) 2 EHRR 387, at para 39.

[89] Just, Marcel A. et al., 'Machine learning of neural representations of suicide and emotion concepts identifies suicidal youth', *Nature Human Behaviour* 1 (12) (2017): 911-919; Torous, John et al., 'Smartphones, Sensors, and Machine Learning to Advance Real-Time Prediction and Interventions for Suicide Prevention: a Review of Current Progress and Next Steps', *Current Psychiatry Reports* 20 (7) (2018): 51.

were able to improve the accuracy of suicide-attempt prediction from 720 days to 7 days before the suicide attempt, by applying a ML algorithm to electronic health records.[90] Again, there is little doubt that improving the accuracy of prediction would be beneficial to suicide prevention. The case of Carol Savage,[91] a woman who died by suicide while detained for treatment under section 3 of the MHA, established that there is an *operational duty* to protect the right to life of a detained patient under Article 2(1) of the ECHR where the hospital knows, or ought to know, of a real and immediate risk to life. The UK Supreme Court has further held in *Rabone v. Pennine Care NHS Foundation Trust*[92] that this operational duty may be owed also to informal patients.[93] Prediction of self-harm and suicidality—whether or not it is achieved via AI—if possible, timely, and accurate would support the operational duty to protect life, which is owed to detained and informal patients by the clinical institutions responsible for their care.

Lastly, predicting *harm to others* means predicting that a person will cause harm to someone else because of their mental illness. In *Osman v. United Kingdom*, the ECtHR held that public authorities must know of a "real and immediate risk to life" of a person by a third party in order to proceed with preventive measures.[94] Among others, Large et al. argue that prediction of dangerousness has very modest scope in preventing violence, and that it unfairly discriminates against the mentally ill.[95] The authors argue that even the best violence prediction tool has very limited utility. They make a strong case about the discriminatory nature of dangerousness criteria:

[90] Walsh, Ribeiro, and Franklin, *op. cit.*
[91] *Savage v. South Essex Partnership NHS Foundation Trust* [2010] EWHC 865 (QB).
[92] *Rabone v. Pennine Care NHS Foundation Trust* [2012] UKSC 2, [2012] 2 AC 72, at para 22: "the operational duty will be held to exist where there has been an assumption of responsibility by the state for the individual's welfare and safety (including by the exercise of control)." See also *Fernandes de Oliveira v. Portugal* [GC] App no 78103/14 (ECtHR, 31 January 2019).
[93] Allen, *op. cit.*
[94] *Osman v. United Kingdom* (2000) 29 EHRR 245, at para 116.
[95] Large, M. M. et al., 'The danger of dangerousness: why we must remove the dangerousness criterion from our mental health acts', *Journal of Medical Ethics* 34 (12) (2008): 877-881. It must be noted that M. Large and C. Ryan also criticise the use of *risk* criteria in the context of suicidality and psychiatric coercion, see their commentary on the *Rabone* case, Large, Matthew, Ryan, Christopher James, and Callaghan, Sascha, 'Hindsight bias and the overestimation of suicide risk in expert testimony', *The Psychiatrist* 36 (6) (2018): 236-237.

> Those accused of a violent crime are deemed innocent until proven guilty, and the state must prove their guilt beyond reasonable doubt. "Better that ten guilty persons escape than that one innocent suffer." Very few statutes permit the incarceration of innocents merely because they might harm others in the future.[96]

Large et al. argue that there are reasons to doubt that accurate prediction of harm to others is even possible. Yet, we cannot predict what AI-mediated prediction might look like in the future. It is indicative that in their scoping review of current ML applications in mental health, Shatte et al. did not report any category which refers to prediction of 'harm to others' (though they did include self-harm and suicide). This could mean that efforts to predict harm to others via ML are *not* currently underway; or, it could mean that prediction of harm others via ML is perceived to transcend the scope of clinical prediction. As 'harm to others' is a *social* occurrence, its prediction might intrinsically differ from efforts to predict psychosis transition, psychosis relapse, or self-harm via ML. Whether prediction of harm to others via ML might be possible depends on the level of surveillance that our societies will decide to accept. Its role in psychiatric coercion will depend on the broader issue of whether risk of harm to others can (ever) justify preventive detention of the mentally ill.

5.6 David Reynolds and the risks of risk

Could AI have saved David Reynolds? Mr Reynolds had been diagnosed with schizophrenia seven years before his death. It was clear that he was having a psychotic relapse on the day of his death. However, he had no history of suicide attempt. He had told the psychiatrist that he did not want to kill himself and was assessed to be a low suicide risk. Was he really at low risk of self-harm or suicide? It is not clear what Mr Reynolds' intentions were when he fell from the window.[97]

[96] Large et al., 'The danger of dangerousness: why we must remove the dangerousness criterion from our mental health acts', *op. cit.*, 879.
[97] See *Reynolds v. The United Kingdom* (2012) 55 EHRR 35, at para 16: the applicant, David Reynolds' mother Mrs Patricia Reynolds, "considered that her son had not attempted to commit suicide but rather had wished to go home and had not realised he was on the sixth floor."

It is also not possible to say whether using AI to monitor his behaviour could have saved his life. However, the ECtHR recognised that "an operational duty arose to take reasonable steps to protect him from a real and immediate risk of suicide and that that duty was not fulfilled."[98] Should reliable ML applications that can predict a suicide attempt be available in the future, would it be a 'reasonable step'—using the language of the ECtHR—for a clinical team to use such applications with psychotic inpatients? If no, for what reasons this would be unreasonable? Potential issues in ML design, such as privacy concerns and the risk of algorithmic bias described above, might constitute some of those reasons. However, it is difficult to answer such questions at this stage. Nonetheless, we can argue that digitally tracking Mr Reynolds' behaviour to assess his risk of suicidality might have helped the clinical team to fulfil their *operational duty* to protect Mr Reynolds' right to life. ML-mediated prediction of suicidality, if possible, timely, and accurate, could have produced real benefits for him, in light of the operational duty to protect his right to life as a voluntary inpatient.

The case of David Reynolds suggests that there are situations where ML-mediated prediction may be beneficial to psychiatric assessment. At the same time, there are risks involved in the logic of risk.

Most of our mental health law frameworks recognise—or, some might say, establish[99]—a dialectic tension between *freedom* and *security*. Freedom here is intended as the liberty of individuals who suffer from mental illness not to be subject to compulsory detention and treatment. Security is intended as the protection from potential harm, which (allegedly) justifies State action in enforcing surveillance, coercion, and detention of the mentally ill. The logic of risk acts as the *medium* between freedom and security. First, the notion of risk mediates between freedom of research—intended as freedom to conduct research as well as liberty to take part in it—and protection of research participants. Second, the notion of risk mediates between the liberty of the mentally ill *not to* be subject to coercion and society and the person's need for security. The risks involved in the logic of risk might be called the *risks of risk*: that in using the logic of risk as a medium between

[98] *Reynolds v. The United Kingdom* (2012) 55 EHRR 35, para 61.
[99] Rose, Nikolas, 'Governing risky individuals: The role of psychiatry in new regimes of control', *Psychiatry, Psychology and Law* 5 (2) (1998): 177-195.

freedom and security, we might fail to make the necessary *nuanced* distinctions between different notions of risk, which serve different purposes. That we might fail to recognise the differences between psychosis risk and risk of harm, and between psychosis prediction and prevention of harm. That in trying to minimise risk and prevent harm we may instead cause harm by means of unnecessary surveillance, coercion, or detention. I argue that in order to maximise the benefits that derive from the expansion of AI into psychiatry we ought to be aware of and minimise the risks of risk.

5.7 Conclusions

This article has claimed that there is a potential for virtuous applications of ML-mediated prediction in mental health. It has suggested that we may have an obligation (a duty?) to promote the benefits that derive from using ML for prediction of psychosis and self-harm, while at the same time avoid the downsides of unnecessary coercion and surveillance. First, I have argued that ML could effectively support the practice of psychiatric assessment. There is little reason to doubt that using ML to improve accuracy in predicting psychosis transition or psychosis relapse could benefit patients and service users. However, before this happens, researchers and RECs ought to ensure that the use of ML applications in clinical research respects the rights and interests of research participants. This includes acknowledging any additional risks posed to participants by the use of ML for data analysis and outcome prediction. It also includes minimising potential risks of research participation, which vary depending on the populations that researchers wish to recruit, their age, and their capacity to consent. Second, I have argued that the notion of *psychosis risk* and the notion of *risk of harm* are different in nature. Establishing someone's risk to transition to, or to relapse into psychosis is not the same as assessing risk of harm. The two practices are distinct, and so should remain when using ML for psychiatric assessment. Third, I have argued that reducing diagnostic uncertainty in psychiatric assessment could benefit the mentally ill. However, using psychosis prediction as a criterion to justify coercion could potentially harm them. The extent to which the use of ML-mediated prediction

might benefit or harm individuals who experience psychosis will depend on: (i) which type of *risk* we are assessing, whether this is psychosis risk or risk of harm, and (ii) what we are trying to predict, whether this a psychosis transition, a psychotic relapse, self-harm and suicidality, or harm to others.

6. CONCLUSIONS

6.1 Psychosis and bioethics

Psychosis is a fascinating subject. Studying psychosis means investigating our self, our perceptions, and our cognition. It means investigating how we define our identity, how we perceive and understand reality, and how the socio-political environment shapes our beliefs and our actions. It involves understanding how our brains work, and questioning the boundaries between what is normal and what is pathological in our cognitive processes. It involves critically appraising how our societies have treated—and continue to treat—those of us whose beliefs and behaviours are somehow different from what is considered normal by culturally established social norms. It also involves questioning the nature of mental illness as well as society's response to the need to mitigate harm that may derive from such illness, both to those who experience psychosis and to society. As Richard Bentall poignantly noticed,

> These explorations have confirmed a view I have held for many years: that psychosis shines a particularly penetrating light on ordinary human functioning. Indeed, I do not think it is an exaggeration to say that the study of psychosis amounts to the study of human nature.[1]

While psychosis remains a fascinating subject and psychotic experiences question our understanding of the human mind, we ought to be reminded of the *suffering* of those who experience psychotic illness. Will knowing more about the neuroscientific and genomic processes behind psychosis help us to ensure that those who suffer from psychotic illness can live a flourishing life? Will having access to such knowledge facilitate their journey towards recovery?

Bioethics is primarily concerned with the identification of the ethical challenges posed by technological innovation in medicine. In this thesis, I have explored such challenges in the context of psychosis. I have addressed the questions: will biomedical innovation and technological convergence be beneficial to those who experience psychosis? If so, how? How do we properly tackle the

[1] Bentall, *Madness Explained. Psychosis and Human Nature*, *op. cit.*, xiv.

moral challenges that arise from the attempt to unveil the neurobiology of psychosis? I have provided some theoretical avenues that might help us to ensure that those who suffer from mental illness can benefit from technological innovation and from the increased understanding of the biology of psychosis that comes with it. In this last section, I shall do three things. First, I summarise the main message of this thesis and discuss two limitations of my work. Then, I reflect on the main messages that emerge from the articles that form the body of the thesis, and I show how my thesis provides an original contribution to the existing literature. Lastly, I discuss some interesting avenues for future research.

6.2 Integrated bioethics in a complex world

The main message that can be drawn from the work presented in this thesis is that we live in a complex world—a world in which the convergence of new technologies requires bioethicists to rethink the ways in which they have tried to tackle the ethical implications of technological innovation in biomedicine. In this thesis, I set out to answer the following research question: What ethical issues arise from the convergence of new technologies—that is, brain imaging, next-generation genome sequencing, and machine learning—in tackling psychosis? What is the most appropriate way to address those issues?

The answer to the first question is, simply put, many. In the thesis introduction and in Article one, I have surveyed the academic literature to identify ethical and legal issues presented by the convergence of neuroscience, genomics, and data science in tackling psychosis. I have shown how in the last years neuroethics, the ethics of psychiatric genomics, psychiatric ethics, and legal scholarship have identified a number of ethico-legal concerns. These range from research governance issues, informed consent, management of research results, of incidental findings, and of neurobiological information to the impact that new technologies have on neuro and genetic essentialism, on social, professional, and clinical relationships, and on how individuals define their identity, make decisions, and understand who they are. What is the most appropriate way to address those issues? In Article one, I have proposed that ethicists should join efforts to tackle

technological convergence. I have *not* claimed that the ELSI approach is ill suited to address those issues. The ELSI approach was indeed developed to promote collaboration across different ethics sub-disciplines. Rather, I have claimed that the ELSI approach is a useful tool to identify ethical, legal, and social concerns. However, I have also claimed that bioethicists should move away from over-specialisation and develop an integrated approach that can put mental health patients' needs at the core of their analysis. Responding to technological convergence requires that ethicists integrate insights from different areas of bioethics, that they translate bioethical principles into the mental health context, and that they proactively try to anticipate future ethical concerns. How can they do that? In Article one, I have proposed one possible solution: we could start by identifying the ways in which people can be harmed or wronged by technological convergence in psychiatry. This means identifying individual and contextual layers of vulnerability. The philosophical notion of vulnerability is an essential conceptual tool to achieve the theoretical integration required by technological convergence. Identifying how individuals might be harmed or wronged by technological convergence in psychiatry, and by the increased understanding of neurobiology that comes with it, can be a first step towards ensuring that technological convergence can benefit patients and help them to flourish.

How can we ensure that technological convergence may truly benefit, and not harm, people who suffer from psychosis? Alongside the claim that we need to develop an integrated approach to bioethics, in Articles two and three I have argued that investigating the impact that new technologies have on the moral worlds of social actors can help bioethicists to reframe normative analysis. I have argued that empirical ethics can complement philosophical analysis in identifying the ethical principles that should guide technological convergence. How did my qualitative work enrich my conceptual analysis? How did it help me to answer my thesis research questions?

In Article two, I have shown that researchers and health care professionals recognise moral obligations that pertain to their professional role in managing access to neurobiological information. Regardless of whether neurobiological information is gathered via next-generation sequencing or brain imaging, or

analysed alongside behavioural data with machine-learning applications, accessing that information could either benefit or harm individuals. The possibility of having access to neurobiological information generates the potential to harm people—thereby exposing their vulnerability—or the potential for them to flourish. My qualitative investigation highlights three main messages in relation to my overarching question. First, neurobiological information is a powerful tool in the process through which individuals who experience psychosis define their identity and establish personal and clinical goals. Second, researchers and health professionals perceive the acquisition of neurobiological information as mostly unproblematic; on the contrary, they think that substantive moral challenges arise from how that information is delivered—that is, communicated and used—in research and in clinical care. Third, reflecting on how neurobiological information is delivered and providing appropriate ethical guidance for such delivery is essential to ensure that technological convergence can truly benefit people who experience psychosis.

In Article three, I have again addressed the question, "how can we ensure that technological convergence may truly benefit, and not harm, people who suffer from psychosis?" by investigating the perspective of another social group: carers of a person suffering from psychosis. The qualitative investigation revealed that, despite the advances in biomedicine we have witnessed in the past decades, mental health carers are angry at how their cared-fors are treated in research and clinical contexts. Carers demand novel research and effective interventions for psychotic disorders. At the same time, carers' hope that technological convergence might ameliorate their cared-fors' life clashes with their fear that technological convergence might produce more harm than benefits. The main message that can be drawn from Article three is that while it is essential to establish clear ethico-legal principles to guide the translation of new technologies in psychiatry, it is also vital to ensure that patients' needs are properly assessed and met. This is not only a theoretical task but also a practical one. Carers are an essential source of knowledge because of the role they play and the value they hold. Whether technological convergence might benefit or harm people who suffer from psychosis depends on whether their values and needs are properly assessed and met.

Lastly, in Article four I have claimed that ensuring that technological convergence can benefit people who suffer from psychosis requires that we establish appropriate legal principles for the regulation of machine-learning applications in psychiatry. I have explored this issue in the specific case of using machine learning for psychosis prediction. I have argued that the regulation of machine learning for psychosis prediction falls within two areas of regulation in the jurisdiction of England and Wales: clinical research and data protection regulation and mental health legislation. First, ensuring that individuals are not harmed by the use of machine learning in clinical research requires that we consider the balance between potential harms and benefits in relation to (1) additional risks introduced by the use of machine learning, and (2) the inclusion of vulnerable populations in research. Second, ensuring that individuals are not harmed by the use of machine learning for risk assessment under mental health legislation requires that we carefully evaluate the use of the notions of 'risk' and 'harm' and that we reaffirm the distinction between psychosis risk and risk of harm; in addition, it requires that we clarify the aims and scope of risk assessment and clinical prediction in psychiatry. Again, in the article I argue that a nuanced understanding of the notions of vulnerability, risk, harm, and prediction is essential to ensure that technological convergence may truly benefit people who suffer from psychosis.

6.3 Two criticisms: A response

Two criticisms can be raised to the work I presented in the thesis. I believe that these criticisms point to two important limitations of my work. I discuss these criticisms here. The first is practical while the second is theoretical.

The first criticism can be formulated as follows. One could argue, if your empirical work is based on the assumption that it is important to investigate relevant actors' perspectives, for what reasons did you not investigate the perspectives of patients and service users? In other words, why did you decide to recruit researchers, health professionals, and carers for your qualitative work but *not* patients and service users? I was asked this question many times during my doctoral studies. I can provide two answers. Again, one is practical and the other is

theoretical. First, there are practical limitations to what can reasonably be achieved by a doctoral student who wishes to conduct qualitative research in NHS facilities in England, especially in a mental health context. In designing ELSI-NAPS, I was faced with the choice of serving as chief investigator of the study—and accepting all the responsibilities that came with the role—or letting my main supervisor act as chief investigator. I chose the former because I believed that acting as chief investigator would be particularly formative in my doctoral journey. Yet, in doing so, I also decided that I would not recruit patients or service users. Even though doctoral students are allowed to serve as chief investigators of NHS studies, it would have been difficult to negotiate ethics approval for a study that recruited psychiatric patients if the chief investigator was a junior academic (not employed by the NHS). This is not to say that it would have been impossible. However, obtaining NHS ethics approval is a long and complicated process. The REC must be satisfied that the chief investigator is able to ensure that participants are appropriately safeguarded. In deciding to recruit non-patient groups, I deemed myself to be in a position where (i) I could take full responsibility for safeguarding research participants, and (ii) I could reassure the REC that I was in a position of effectively doing so. The second answer is theoretical. It has to do with the conceptual design of my research. In one sentence, I *did not wish* to investigate patients and service users' perspectives as these fell outside the scope of my research questions. As I outlined in previous sections of this thesis, the ELSI debate is particularly focused on the identification of moral principles and obligations that pertain to professionals in research and in clinical care. Investigating their perspectives was the aim of my work. In addition, recruiting carers allowed me to investigate cultural understandings beyond the research and clinical community, while ensuring that I was able to safeguard participants to a degree compatible with my research experience. My decision not to investigate patients' perspectives *does not entail* that these are not important or not worthy of qualitative investigation. Yet, the practical and theoretical boundaries of my research meant that I would not recruit patients and service users in my doctoral fieldwork.

The second criticism can be formulated as follows. One could say, in Article one you argue that the notion of vulnerability is an essential philosophical tool to

achieve the theoretical integration of the ELSI discourse. In doing so, you use the notion of *layers* of vulnerability developed by Florencia Luna to identify factors that render individuals who (may) suffer from psychosis vulnerable. You acknowledge that Luna's notion of layers of vulnerability is an attempt to criticise population-based accounts of vulnerability used in research ethics.[2] Yet, in Article four, when you investigate the regulation of machine learning in clinical research, you discuss how regulation shapes the conduct of research with vulnerable groups—such as minors and incapacitated adults. Why is that so? Is there not a contradiction between the notion of vulnerability you use in Article one and your discussion of vulnerable groups in Article four? This is a legitimate concern.

I argue that there is no contradiction in my discussion of vulnerability in Article one and Article four. First, my theoretical approach is the same in both articles. In both articles, I identify factors that may increase someone's vulnerability, understood as someone's likelihood of being harmed or wronged. These factors include age and mental capacity, though I do not argue that these factors *intrinsically* render someone vulnerable. I do not support a population-based account of vulnerability, though I believe that, for instance, not having the mental capacity to provide consent should raise concerns in terms of someone's likelihood of being harmed or wronged by participation in research. Second, Article four is a legal article. In Article four, I discuss how *current* regulation might shape the use of machine learning in clinical research. Clinical research regulation in England and Wales sets out specific requirements with regard to the risk-benefit ratio for different research populations.[3] Minors and incapacitated adults are (legally) considered specific research populations in England and Wales.[4] It could be argued that regulation in this jurisdiction still displays a population-based account of vulnerability. Indeed, Bracken-Roche et al. have shown how research ethics guidelines worldwide still identify vulnerable groups.[5] A critical evaluation of the theoretical underpinnings of regulation is paramount. Yet, when discussing how

[2] See Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*
[3] See Article four in this thesis, section 5.4, "Regulating clinical research".
[4] For instance, healthcare research with persons lacking capacity to consent is governed in England and Wales by the Mental Capacity Act 2005.
[5] Bracken-Roche et al., 'The concept of 'vulnerability in research ethics: an in-depth analysis of policies and guidelines', *op. cit.*

current regulation might shape the use of machine learning in England and Wales, I am bound to talk about vulnerable research populations. This does not imply that I endorse a population-based account of vulnerability, so long as my theoretical approach is not population-based and so long as I make my approach explicit, which I have also done in Article one. At the same time, the *tension* between a philosophical understanding of vulnerability and the notion of vulnerability used in regulation generates some theoretical challenges. I discuss these challenges in the next section.

6.4 Vulnerability and psychiatry: Challenges and opportunities

The expansion of neuroscience and genomics into psychiatry has the potential to increase our understanding of the neurobiology of psychosis and to generate new ways of preventing, diagnosing, and treating psychotic illness. Along with potential benefits, this endeavour could generate harms to those who (may) suffer from mental illness. The ELSI discourse is a powerful tool to identify potential harms and benefits. Yet, as I have argued in Article one, the ELSI discourse alone is *not enough* from the standpoint of bioethics. We must find a way to integrate insights from different areas of ELSI research while keeping patients and service users' needs at the centre of our analysis. The philosophical notion of vulnerability seems to be an appropriate conceptual tool to achieve this theoretical integration. At the same time, the notion of vulnerability has a long and, to a certain extent, troubled history in research ethics and in psychiatry. Reflecting on this history can help us to identify theoretical and practical challenges as well as potential avenues for future research.

Can a layered, contextual, and relational notion of vulnerability as developed in vulnerability theory and the notion of vulnerable populations as used in current research regulation go together? Probably not. Is a synthesis between these two notions possible? Probably yes.

First, it will be important to investigate *if* and *how* the universal idea of vulnerability as a defining feature of the human condition—as developed,

eminently, by Martha Fineman[6]—can be compatible with the attempt to identify how people are rendered (more or less) vulnerable by individual and contextual factors. Is the universal notion of the vulnerable subject developed by Fineman compatible with the notion of layers of vulnerability developed by Luna? Is affirming that, as embodied beings, we are *all* vulnerable compatible with the effort to identify how those in a certain condition or situation—for instance, a young individual experiencing psychosis who is offered to take part in neuroimaging research—can be *rendered* vulnerable? Is saying that we are all vulnerable compatible with saying that certain people may be rendered particularly vulnerable by individual and contextual factors? This is a first important avenue for future research.

Second, it will be important to investigate the conceptual bases of current research regulations to ensure that an appropriate and nuanced notion of vulnerability can shape the conduct of psychiatric research. Not only is this a theoretical task but also a political one. Population-based accounts of vulnerability have shaped research regulation for decades, at least since the publication of the Belmont Report in 1979.[7] Individuals suffering from mental illness have traditionally been considered a vulnerable population. Indeed, the current critique of population-based accounts of vulnerability began as an attempt to show how such accounts are ill suited to promote harm minimisation and often result in the unfair exclusion of certain social groups from participating in research.[8] While I agree that population-based accounts of vulnerability ought to be amended in regulation, in this thesis I have argued that identifying individual and contextual sources of vulnerability is essential to ensure that those who experience psychosis are appropriately safeguarded, in research and in clinical care. How do we amend regulation while maintaining a (layered) notion of vulnerability? Scholars in

[6] Fineman, *op. cit.*
[7] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *op. cit.* See also Ries, Nola M. and Thomson, Michael, 'Bioethics and Universal Vulnerability: Exploring the Ethics and Practices of Research Participation', *Medical Law Review* 28 (2) (2020): 293-316; Luna, 'Elucidating the Concept of Vulnerability: Layers Not Labels', *op. cit.*
[8] Levine et al., *op. cit.*

bioethics have already started to address this issue.[9] I believe this to be a second important avenue for future research that emerges from my work.

How should we understand vulnerability in psychiatry? One further suggestion might be drawn from my work. It is a methodological suggestion and not a conceptual one: we could work towards developing a *participatory* account of vulnerability in psychiatry. Participatory research is broadly defined as the attempt to involve participants as active contributors in the design, conduct, and dissemination of research.[10] If we wish to find out *how* people who experience psychosis might be rendered vulnerable in relation to research and care, why not discuss this with the people involved in these practices?

I did not develop a participatory account of vulnerability in this thesis. I did not explicitly discuss with ELSI-NAPS participants what they thought that vulnerability might mean. Yet, I discussed benefits and harms of technological innovation. The findings I presented suggest that empirical bioethics could be an appropriate methodology to develop a participatory account of vulnerability in psychiatry. Researchers and health professionals in ELSI-NAPS discussed their obligations in managing access to neurobiological information in relation to the identity impacts that this could have on patients and service users. Their main ethical concern was to make sure that having access to neurobiological information could benefit, and not harm, those who experience psychosis. Investigating their perspective could thus be important to establish what vulnerability means in psychiatry. The same is valid with regard to carers. Carers' moral outlook has epistemic value in identifying the needs of their cared for. Carers are in a position to identify sources of vulnerability because of the role they fulfil and because of the values they cultivate. Lastly, if we wish to know what vulnerability means in psychiatry, why not ask patients and service users directly? While it is legitimate to think that age and illness can affect someone's capacity to take part in research, assuming that those who experience psychosis cannot contribute to the debate on

[9] See for instance the integrative and functional account of vulnerability proposed by Racine, Eric and Bracken-Roche, Dearbhail, 'Enriching the concept of vulnerability in research ethics: An integrative and functional account', *Bioethics* 33 (1) (2019): 19-34.

[10] See for instance Friesen, Phoebe et al., 'Measuring the impact of participatory research in psychiatry: How the search for epistemic justifications obscures ethical considerations', *Health Expectations* (2019): 1-8.

vulnerability would mean, at best, refusing to recognise the epistemic value of their lived experience for ethical inquiry and, at worst, accepting the very population-based presumption of incapacity that we are trying to refute.

6.5 ELSI-NAPS: Positives, pitfalls, and lessons learned

Before I go on to discuss the theoretical implications of my findings, I wish to discuss briefly some methodological implications of my empirical work. Conducting an empirical ethics study in the NHS was not an easy task, though a formative one. Some things went well, others went wrong, and I feel I have learned a lot from both.

Social research has different timeframes from theoretical research. Obtaining ethics permission to conduct ELSI-NAPS was a long process that took almost a year from the initial design to the start of recruitment. This process involved obtaining clearance from four institutional actors: the University of Manchester, the NHS REC committee, the Health Research Authority, and Greater Manchester Mental Health NHS Foundation Trust (GMMH). The REC submission included a form of approximately 80 items and a 33-page research protocol to be submitted along with 27 attachments. After ELSI-NAPS was granted favourable ethical opinion, any change in study documentation had to be submitted to the REC. I had to submit a new study leaflet to the REC in December 2017 and this was classified as a substantial amendment. In order to complete participant recruitment, I also had to postpone the end-of-study date twice, once in July 2018 and again in October 2018. In both occasions, these were classified as non-substantial amendments that had to be submitted to the REC. Each of these amendments had to be negotiated with the University of Manchester and with GMMH as the lead recruitment NHS site.

Recruiting participants to take part in social research is also a long and complicated task. Being allowed to recruit after ethics review is only the starting point of recruitment. What follows is months or years—in my case, 16 months—of letters, emails, phone calls, visits, and travels. This process was as exciting as it was tiring. Only about 20% to 30% of the people I invited to take part in the research

returned my messages. Less than that agreed to take part. Over 16 months from September 2017 to January 2019, I travelled across England to interview researchers in group A; I contacted and visited community mental health services across GMMH to present my research to professionals in group B—Greater Manchester is a huge metropolitan area and at the same time unbelievably friendly—; I visited charities and mental health (carers) groups across Greater Manchester to present ELSI-NAPS. This is something that social researchers are trained to face, accept, and plan accordingly. For a postgraduate researcher in bioethics with some experience of qualitative work, it was an extremely formative and humbling experience.

Not only has social research different timeframes from theoretical research. Social research requires appropriate *skills* and training. This is true for data collection and for data analysis. First, conducting qualitative research in mental health requires negotiating skills, especially to gain access to NHS facilities. Second, conducting interviews and focus groups requires skills and training as well as careful planning. Interviews and focus groups are sometimes cancelled. The reality of mental health care—whether one looks at it from the perspective of researchers, health professionals, or carers—is a hectic one. Collecting participant information and qualitative data requires data management skills and a thorough knowledge of privacy and confidentiality requirements as well as applicable laws. Laws, indeed, can change. When I started designing ELSI-NAPS at the end of 2016, the study had to comply with the Data Protection Act 1998. The General Data Protection Regulation (GDPR) was implemented across the EU on 25 May 2018 and the new Data Protection Act 2018 received Royal assent in May 2018. This changed how I could handle research data, and I had to produce a data management plan in January 2019. Third, qualitative data analysis is a long and complicated process in which a researcher must dive into the data to make sense of what is being said. The goal of this process is to ensure that data are properly analysed and described while minimising *bias* in the interpretation of the arguments expressed by participants.[11] To avoid bias, careful oversight by other researchers—in my case, my supervisors—is essential.

[11] Corbin and Strauss, *op. cit.*

The argument I am trying to make is that empirical ethics requires time, skills, and shared efforts by a team of researchers to yield valuable results. These requirements differ from what is required of purely theoretical research. What did I learn from conducting ELSI-NAPS? I learned a lot about research methodology, which is (allegedly) the main goal of a doctorate. I passed NHS ethics review. I completed recruitment and I gathered rich data. I understood a lot about my field of inquiry by discussing with people who can provide an informed non-ethicist perspective on it. I learned that specific methodologies are dictated by specific research questions. In other words, conducting empirical ethics means affirming the relevance of social research questions to the normative discourse. Most importantly, I learned one important meta-ethical commitment that justifies empirical ethics: to give a voice to relevant actors when deliberating on complex moral issues. Even though conducting empirical research requires additional time and training, I believe that the methodological and practical skills to be gained from such endeavour make it extremely valuable for a doctoral student in bioethics. I shall now discuss how I approached the issue of combining empirical data and normative theory in my doctoral work.

6.6 Empirical ethics: Empirical data and normative theory

How do we combine empirical data and normative theory in empirical ethics? How are qualitative findings relevant to the normative discourse? In this section, I consider these issues in relation to the ELSI-NAPS findings I presented in Articles two and three.

The theoretical possibility of empirical ethics and the question of how to combine empirical data and normative theory are two separate, though interconnected, issues. As I outlined in the introduction, the question around the epistemological value of empirical (bio) ethics has characterised the ethics debate for a few decades.[12] In recent years, the debate appears to have shifted from the question of *whether* empirical bioethics is theoretically justifiable to *how* to combine the descriptive and the normative—or, empirical data and normative

[12] See Borry, Schotsmans, and Dierickx, *op. cit.*

theory—in empirical bioethics.[13] In a volume edited by Widdershoven et al., several scholars presented examples of how they combined empirical work and normative theory in conducting empirical ethics in psychiatry.[14] Approaches to address the issue have bloomed. For instance, a number of ethicists have recently explored the possibility to develop *experimental philosophical bioethics*, which draws from experimental philosophy to complement empirical bioethics in gathering and analysing empirical data in relation to normative theory.[15] A systematic review of empirical bioethics methodologies has identified at least 32 different methodologies used in the literature.[16] The authors classify most of these methodologies as either 'dialogical' or 'consultative'. Briefly, dialogical approaches aim to reach normative conclusions through dialogue between researchers and participants. In consultative approaches, participants do not take part in the process of forming normative conclusions; they are only consulted about ethical issues.

By referring to this classification, the approach I used in Articles two and three can be classified as 'consultative'. In ELSI-NAPS, I did not reach normative conclusions through dialogue with participants. Instead, as required by grounded theory, I investigated the perspectives of social actors while trying to minimise my influence on participants' views and personal bias during data analysis. I offered a snapshot of participants' moral life through instruments offered by social research. Further, I did not draw strong normative conclusions from my qualitative data. Yet, I claimed that these data are of epistemic value in reorienting normative theory. I conducted what Raymond De Vries has called *descriptive ethics* or sociology 'in' bioethics.[17]

Should empirical bioethics necessarily combine empirical data and normative theory? I contend that it should not. Is descriptive ethics part of empirical bioethics? I argue that it is. First, if we require *all* empirical bioethics to combine empirical data and normative theory, then we risk excluding from empirical

[13] See, for instance, the interesting volume recently edited by Ives, Jonathan, Dunn, Michael, and Cribb, Alan (eds.), *Empirical Bioethics. Theoretical and Practical Perspectives* (Cambridge: Cambridge University Press, 2017).
[14] Widdershoven et al. (eds.), *op. cit.*
[15] Earp, Brian D. et al., 'Experimental Philosophical Bioethics', *AJOB Empirical Bioethics* 11 (1) (2020): 30-33.
[16] Davies, Ives, and Dunn, *op. cit.*
[17] De Vries, *op. cit.*

bioethics those sociological approaches—for instance, grounded theory—whose aim is to describe social phenomena while not directly formulating normative arguments. Yet, if that is so, how are sociological methods relevant to bioethics? When and how can they be used in empirical bioethics? John McMillan has provided an interesting perspective on this issue. He argues that empirical methods are relevant to medical ethics when they serve the purpose of advancing our understanding of moral issues in healthcare,

> While medical ethics must draw on a range of methods and disciplines, good medical ethics uses these methods to further our understanding of, and decisions about, important moral issues in medicine and healthcare. That means all approaches to medical ethics, be they empirical, legal, sociological, theological or philosophical should aim at being practically useful.[18]

Following McMillan, qualitative research is relevant to medical ethics—and, I argue, can be considered part of empirical bioethics—when it serves the purpose of shedding light on moral issues in healthcare and of helping us to frame the normative discourse. This, I argue, even when normative conclusions are not directly drawn from qualitative work, whose purpose is often to *describe* how individuals understand moral challenges rather than to *prescribe* what individuals ought to do through moral deliberation.

If descriptive (bio) ethics, or sociology 'in' bioethics can be legitimately considered part of empirical bioethics, how does it differ from medical sociology? The answer lies in McMillan's argument. Descriptive ethics can be considered empirical bioethics when it is practically useful to understanding moral issues in health care. It differs from medical sociology in that (i) the *object* under investigation must involve ethical issues in health care, and (ii) the *aim* of the research should be to increase our understanding of the normative discourse. Yet, when we use methods adopted from the social sciences—such as grounded theory—we are *methodologically* conducting sociological research. Descriptive

[18] McMillan, John, 'Good medical ethics', *Journal of Medical Ethics* 44 (8) (2018): 511-512.

(bio) ethics and medical sociology are intertwined: not all medical sociology is, obviously, descriptive ethics, but descriptive ethics that uses methods drawn from medical sociology to investigate moral issues in health care and to reframe the normative discourse should, I argue, be considered part of empirical bioethics.[19]

In ELSI-NAPS, I conducted sociological work to shed light on the ethical debate around the impact of neuroscience and genomics on how we understand, diagnose, and treat psychotic illness. As I showed in Articles two and three, my qualitative findings can help us to reframe normative analysis around the ethical challenges of technological convergence in psychiatry. In the next section, I shall briefly summarise how.

6.7 Identity and bioethics: The value of life and the life of values

In questioning the impact of technological innovation in medicine, bioethics has focused on the value we attribute to life. The beginning of life, the end of life, and how we give value to life in face of the transformations of our everyday experience introduced by technology have been the original—and, in the past decades, the traditional—locus of bioethical investigation. Bioethics investigates the value of life.[20] Moral philosophy has shaped bioethical arguments. Consequentialists, deontological, principle-based, virtue and care ethics approaches have shaped discussion about how we *should* understand life and how we *ought to* respect persons and the value they attribute to life. The more technology increases our ability to comprehend the human body and the deeper genomics digs into the secrets of our biology, the more we need guidance on how to handle that knowledge and on how to shape our lives in response to it. The more technology increases our understanding of the human brain the more urgent become our questions around the human mind. In questioning the value of life in face of technological development, bioethics has investigated the meaning of personal identity. What is a person? What does it mean to respect persons and the value they attribute to their lives? What defines a person's identity, or, what makes me 'me'?

[19] See for instance Buchbinder and De Vries, *op. cit.*
[20] Harris, John, *The Value of Life. An Introduction to Medical Ethics* (London and New York: Routledge, 1985).

The way in which my empirical findings can help us to orient normative analysis concerns how we approach the issue of personal identity. Not only does genomics prompt us to ask *who* we should bring into existence and *how* we should conduct our lives in face of the increased knowledge about our bodies. The convergence of neuroscience and genomics prompts us to ask how knowing about the neurobiological substrates of our *mental states* can influence how we understand—and construct—our identity. Researchers and health professionals in ELSI-NAPS argued that neurobiological information is a powerful tool in the process through which individuals define their identity and establish clinical and personal goals. This powerful tool needs appropriate ethical guidance on how it is to be used. We might have known that already, and scholarly efforts are already underway to provide that guidance. Yet, participants in ELSI-NAPS stressed that, from their perspective, what is morally problematic is how neurobiological information is *delivered*—that is, communicated and used, rather than acquired—to those who may suffer from psychosis. The reason for this is to be found in the fact that having access to bio-information influences how people shape their identity or, in other words, how they understand themselves. There is the locus for potential benefits and potential harms, and there is where the modalities of such delivery acquire moral salience. The potential to benefit or harm people resides in how professionals shape the discourse around neuroscience and genomics in relation to how those who (may) suffer from mental illness narratively construct their identities.

This has implications for the bioethics discourse around identity. Bioethics has extensively focused on how our philosophical understanding of personal identity—and, for instance, the notion of non-identity[21]—ground our moral obligations towards present and future generations. This is evident in reproductive ethics and in population ethics as well as in debates around human enhancement.[22] So conceived, the philosophical discussion on personal identity has shaped the

[21] See Parfit, Derek, *Reasons and Persons* (Oxford: Oxford University Press, 1984).

[22] In relation to the notion of personal identity and the non-identity problem in bioethics, see the interesting article by Bennett, Rebecca, 'When intuition is not enough. Why the Principle of Procreative Beneficence must work much harder to justify its eugenic vision', *Bioethics* 28 (9) (2014): 447-455. For an overview on the debate around human enhancement see Savulescu, Julian and Bostrom, Nick (eds.), *Human Enhancement* (Oxford: Oxford University Press, 2009).

debate around the moral principles that should govern the use of bio-information in medicine. While I recognise that reflecting on the philosophical notion of personal identity is essential, I contend that advances in neuroscience and genomics call bioethics to investigate not only how identity is philosophically understood but also how it is narratively constructed. Using Parfitian terms, even if we reject the person-affecting view—that is, the view that what is bad must be bad for someone[23]—and argue that bioethics ought to be concerned with acts that might not harm anyone in the future, we can still recognise that, here and now, person-affecting problems evolve as our technology and societies evolve. Person-affecting problems—that is, problems that affect real persons—must be recognised to include how people narratively construct their identities: in other words, how people understand who they are. I argue that bioethics ought to reflect on personal identity *and* on narrative identity. This is not to say that scholars in bioethics are not already doing so, but that my findings strongly support the necessity of bioethical investigation on narrative identity in order to ensure the ethical translation of neuroscience and genomics into mental health.[24]

The way in which my empirical findings can help us to orient normative analysis also concerns how we understand moral values. If exploring relevant actors' perspectives can help us to frame ethical theory, then not only should bioethics investigate the value of life but also *the life of values*. By life of values, I mean how people perceive moral challenges and ethical obligations and how they construct and negotiate the values that guide their actions in the practice of research and care. Further, if qualitative research and empirical bioethics have epistemic value, then bioethics must accommodate their findings so that technological innovation might effectively benefit and not harm those who experience mental illness. Respecting persons might also mean that we *ought* to investigate what people think of, and how they can properly enact those principles and obligations that are identified in normative theory. Understanding the value of life means that we ought to investigate the life of values.

[23] Parfit, *op. cit.*, 363.
[24] See for instance Postan, *op. cit.*; Parens, Erik, *Shaping Our Selves: On Technology, Flourishing, and a Habit of Thinking* (New York: Oxford University Press, 2014).

6.8 Care ethics: Towards a theory of care in psychiatry

In Article two, I have shown how a number of researchers and mental health professionals understand the moral challenges of acquiring, communicating, and using neurobiological information on psychosis in research and in clinical care. I have shown how they frame their moral obligations around the impact that having access to bio-information can have on *how* those who suffer from psychosis understand themselves. I have claimed that these findings prompt us to reconsider the relevance of narrative identity for normative analysis. The findings from the focus groups I conducted with carers of a person suffering from psychotic illness, which I presented in Article three, prompt us to do something further. These findings suggest that we must work towards developing an appropriate *theory of care* in psychiatry.

Technological innovation holds promise to transform the care of those who suffer from psychotic illness. At the same time, the carers I spoke to strongly demanded novel research and effective interventions that might help their ill relative to live a flourishing life. They expressed anger at their (relative's) present situation, hope that technological innovation might ameliorate their (relative's) life and fear that it might not be so, and that technological innovation could instead exacerbate ethical issues in psychiatry. There appears to be a disconnection between the promise of technological innovation and carers' ambivalent response. Why is that so? This disconnection could be only chronological. It could be that carers must wait until technology brings about its promised revolution. This is a possibility. I have supported a different hypothesis. I have argued that carers' narratives reveal a *different outlook* on the moral challenges of technological innovation in psychiatry. This also explains why traditional ethical issues regarding the implementation of neurobiological approaches to psychosis—such as capacity, coercion, and ethical issues in handling bio-information—were almost absent from carers' discussion. Carers' outlook has epistemic value because their situation and the values they cultivate allow them, and allow us, to identify some of their cared fors' needs. Carers' outlook has epistemic value because it helps us to realise that technological innovation, and the increased understanding of the neuroscience and genomics of psychosis that comes with it, can *truly* benefit those who suffer from mental illness

only if their caring needs are appropriately assessed and met. Technological innovation can truly benefit those who suffer from psychosis only if it helps us to respond to their needs.

We need a theory of care in psychiatry so that we can recognise the (epistemic) value of the practice of care and recognise care as both practice and value.[25] I did not develop a theory of care in psychiatry in this thesis. Yet, my work prompts me to reflect about how this theory could be constructed.

First, the epistemic value of carers' moral outlook can be properly understood only within an ethics of care. By 'ethics of care', I mean an ethical framework that can allow us to identify the defining features of care as both a practice and a value. As I have argued in Article three, such ethical framework could benefit from integrating some of the conceptual tools developed within the tradition of 'care ethics' by scholars such as Virginia Held and Joan Tronto. In this sense, I argue that a theory of care in psychiatry should be grounded in the ethics of care. Grounding a theory of care in psychiatry in the ethics of care would allow us to identify the normative character of vulnerability: care can be understood as a response to human vulnerability. As Joan Tronto argued while discussing what should characterise the ethics of care,

> Responsiveness signals an important moral problem within care: by its nature, care is concerned with conditions of vulnerability and inequality. Caring is by its very nature a challenge to the notion that individuals are entirely autonomous and self-supporting. To be in a situation where one needs care is to be in a position of some vulnerability.[26]

Care, understood as practice and value, is a response to human vulnerability that allows us to *identify* someone's needs and that *justifies* our moral obligation to respond to those needs. Grounding a theory of care in psychiatry in the ethics of care would allow us to recognise the epistemic value of carers' outlook as *essential* to identifying benefits and harms of technological innovation. Those benefits and

[25] See 'Care as Practice and Value' in Held, *op. cit.*, 29-43.
[26] Tronto, *op. cit.*, 134.

harms are essentially linked to whether the needs of those who suffer from mental illness are appropriately assessed and met. Second, not only should a theory of care in psychiatry be an ethical theory but also a *political* one. The ethics of care is intrinsically political.[27] It requires that we rethink—and restructure—our societies in recognition of the value and practice of care. The carers I spoke to in ELSI-NAPS supported the same argument. They demanded a substantial restructuring of how neuroscientific and genomic research are conducted and of how psychiatry is practised in recognition of their role as carers. They demanded a substantial restructuring of society in recognition of their role and values. Not only did they request this: they *demanded* it. Mental health carers' demands should qualify a theory of care in psychiatry as an ethical and political theory.

A theory of care in psychiatry so constructed would prompt us to ask the question, is medical ethics actually a barrier to scientific development and medical innovation? More precisely, *how* can medical ethics be a facilitator and *not* a barrier to scientific development and medical innovation? Classifying those who suffer from mental illness as a vulnerable population has often resulted in their *unfair* exclusion from research.[28] Further, there are problems in the enactment of *confidentiality* in mental health. Mental health carers have often complained that they are excluded from important decisions regarding their relatives because of an uncritical reference to confidentiality.[29] They feel that even if they are an essential part of the community treatment model they are denied access to vital information and treatment decisions because of the requirements of confidentiality.[30] In Article three, I have formulated the hypothesis that an uncritical reference to *autonomy* in understanding confidentiality might not provide appropriate avenues to solve this conflict. Uncritically focusing on autonomy in psychiatry runs the risk of disrupting caring relationships and thus of producing more harms than benefits. Confidentiality may be more properly understood—and enacted—by reflecting on the practice and value of care. Here, I argue that a theory of care grounded in the ethics of care, and understood as both ethical and political, could help us to ensure

[27] Ibid., 3.
[28] Levine et al., *op. cit.*
[29] Szmukler and Bloch, *op. cit.*
[30] Askey et al., *op. cit.*

that medical ethics is a facilitator, and not a barrier, to scientific development and medical innovation in psychiatry.

6.9 The rise of artificial intelligence

When I first enrolled as a doctoral student, machine learning and artificial intelligence were not a widespread topic of ethico-legal discussion. Psychosis prediction and psychosis risk identification were—and, in clinical care, they still are—performed via clinical interview.[31] The ethico-legal debate was mostly focused on the ethical implications of identifying psychosis risk and on what should follow such identification in terms of disclosure and offer of care.[32] Machine-learning methods and artificial intelligence were used in a (relatively small) number of research studies to classify clinical groups and to improve the accuracy of prediction.

The situation has changed rapidly in the past years. Artificial intelligence has bloomed in countless ways. This is true for numerous strands of medicine as, more in general, for society. The ethico-legal implications of the exponential growth in the use of machine learning and artificial intelligence are *now* a widespread topic of discussion. Bioethics and neuroethics have followed suit. In an article published in *Nature* in 2017, a group of researchers in bioethics and neuroethics identified four key challenges, or four main areas of ethical concern at the interface between the development of neuro-technologies and that of artificial intelligence: (i) *privacy and consent*; (ii) *agency and identity*, meaning the impact that neuro-technology and artificial intelligence could have on how we understand ourselves and our actions; (iii) *augmentation*, meaning the ethical, legal, and social implications of augmenting our (cognitive) capacities; and (iv) *bias* in the development of machine learning algorithms.[33] Digital ethics and the ethics of artificial intelligence are developing at such a fast pace that this fact has prompted scholars to question the *ethics of AI ethics*.[34] As our physical and digital lives

[31] Fusar-Poli et al., 'The psychosis high-risk state: A comprehensive state-of-the-art review', *op. cit.*
[32] Appelbaum, 'Ethical Challenges in the Primary Prevention of Schizophrenia', *op. cit.*
[33] Yuste, Rafael et al., 'Four ethical priorities for neurotechnologies and AI', *Nature* 551 (7679) (2017): 159-163.
[34] Schuklenk, *op. cit.*

become more and more intertwined, philosophers have started describing our condition as 'onlife'.[35] Artificial intelligence is on the rise and so is the ethico-legal debate around it.

I had not anticipated such developments when I began my doctorate. The report I wrote at the end of my first year as a doctoral student contained close to no reference to machine learning and artificial intelligence—save for the indication that machine-learning based psychosis prediction was among the most interesting avenues for the translation of neurobiological findings in psychiatric care. However, artificial intelligence became so prominent in ethico-legal discussion that I decided to focus my legal analysis on it. As in other strands of medicines, machine learning is now used in countless ways in mental health, though a recent systematic review has shown how the use of machine learning in mental health is still mostly confined to research.[36] I had originally intended to investigate how biotechnology regulation and mental health law shape the conduct of neurobiological research on psychosis and the translation of research findings in clinical care. The rise of artificial intelligence prompted me to investigate how the use of machine learning for psychosis prediction might be regulated in clinical research and in mental health care in the jurisdiction of England and Wales. Given the scope of regulation in this jurisdiction, I decided to focus on the issue of *risk* and on that of *coercion* and civil detention of the mentally ill.

Regulating artificial intelligence requires that we reflect on the challenges that the increased availability of (bio) information poses to our legal systems. We live in information-loaded societies and we must produce new rules on how to cohabitate the *infosphere*.[37] As I have tried to show in Article four, the rise of artificial intelligence poses practical challenges to legal systems and theoretical challenges to legal theory. Beyond the issue of data protection, the historical relevance of the GDPR is that it is one of the first legal instruments to make provisions regarding automated data processing and automated decision-making.[38] Until specific legal instruments are produced that regulate the use of artificial

[35] Floridi, Luciano (ed.), *The Onlife Manifesto. Being Human in a Hyperconnected Era* (Springer, 2015).
[36] Shatte, Hutchinson, and Teague, *op. cit.*
[37] Floridi, *The Fourth Revolution. How the Infosphere Is Reshaping Human Reality*, *op. cit.*
[38] See Information Commissioner's Office, *Guide to the General Data Protection Regulation* (2018).

intelligence in the several domains of our lives—including psychiatry—we will need to understand *how* artificial intelligence falls within other legal domains in light of the social activities it transforms. This is what I have tried to do in Article four. Regulating machine learning in psychiatry means investigating how it might affect the practice of mental health research and the delivery of mental health care as they are regulated in England and Wales. Yet, in addressing the issues of risk and coercion in Article four, I have barely scratched the surface of this novel area of legal theory.

Regulating artificial intelligence involves inquiring how artificial intelligence might be regulated by existing legal instruments, or whether new legal instruments are required at a domestic or international level. Regulating artificial intelligence *in psychiatry* requires that we investigate how it might change psychiatry in light of how this is regulated in a given jurisdiction. In the case of psychosis, I have argued that this involves investigating how the use of machine learning might pose additional *risks* to those who participate in research with reference to data acquisition, data analysis, and outcome prediction. Further, I have argued that the way in which psychiatry is shaped by mental health legislation will influence how artificial intelligence is used to identify psychosis risk and risk of harm, and to make predictions about what might happen to those who suffer from mental illness. Risk of harm, prediction, and coercion are deeply intertwined in mental health legislation in England and Wales, as they are in other jurisdictions. The rise of artificial intelligence poses particular legal challenges to how we regulate psychiatry also because, unlike in other medical domains, the question of whether coercion and involuntary hospitalisation are *ever* justified is still hotly debated.[39] Yet, further research is needed to understand the impact of artificial intelligence within and *beyond* the issue of coercion.

6.10 Originality and directions for future research

How should bioethicists address the ethical issues that arise from technological convergence in the context of psychosis? How can we ensure that technological

[39] Szmukler, *op. cit.*

convergence may truly benefit, and not harm, people who suffer from psychosis? The original contribution provided by this thesis lies in the recognition that we live in a world that is becoming increasingly complex. It lies in the call for bioethicists to develop an integrated approach that can tackle the ethical issues presented by technological convergence, and in providing evidence for the need to do so. As I have argued in this thesis, bioethicists can do that by promoting interdisciplinary collaboration and by focusing on the individual and contextual sources of vulnerability that put those who experience psychosis at risk of being harmed or wronged. Bioethicists *should* do that by investigating the insights that social actors—researchers, health care professionals, carers, patients, and service users—can provide to philosophical and normative analysis. They should reflect on the identity impacts that having access to neurobiological information can have on those who experience psychosis. They should reflect on carers' demand for effective interventions and for a greater attention to patients' values and needs. Lastly, the original contribution provided by this thesis lies in the call for bioethicists to contribute to establishing clear legal principles to tackle machine-learning-driven technological convergence. These legal principles should be formulated to ensure that new technologies and novel predictive tools could be used to ameliorate the lives of those who suffer from psychotic illness, to support their recovery, and to help them to flourish.

Where does my work lead in terms of future research? I believe there are five directions for future research that can be drawn from this thesis. (1) To explore theoretical avenues—other than vulnerability—that can provide some common ground for ethicists to join efforts and to build an integrated approach to bioethics. (2) To investigate the philosophical foundations of the notion of vulnerability and to clarify how the notion of vulnerability can be used in psychiatry. (3) To formulate ethical guidance on how neurobiological information ought to be acquired and delivered in the context of psychosis, paying particular attention to the impact that having access to neurobiological information can have on the narrative identity of people who experience psychosis. (4) To develop a theory of care in psychiatry. (5) To investigate the challenges that the use of machine learning and artificial intelligence in psychiatry poses to our legal systems. Drawing from the arguments

presented in the conclusions of this thesis, I shall now outline and summarise these five directions for future research.

First, the ELSI discourse along with the contributions that bioethicists, neuroethicists, and legal scholars provide to it remain a powerful tool to identify the ethical and legal challenges arising from neuroscientific and genomic approaches to psychosis. I *did not* argue that the ELSI discourse is not essential in this endeavour. ELSI research should continue to identify ethico-legal challenges as clinical neurosciences and psychiatric genomics unveil the complexities of the neurobiology of psychosis. Yet, as neuroscience, genomics, and data science converge, I argue that ethicists should join efforts and promote collaboration to tackle technological convergence.

Second, if the notion of vulnerability is an important tool to achieve the integration of different ELSI perspectives, historical and theoretical problems with this notion require us to rethink its philosophical foundations. Future research should address (i) how the universal idea of vulnerability as a defining feature of the human condition can be compatible with the attempt to identify how people are *rendered* vulnerable by individual and contextual factors, and (ii) how to ensure that nuanced, non-population-based accounts of vulnerability might shape the conduct of psychiatric research. As a methodological suggestion, I argue that future research could work towards developing a *participatory* account of vulnerability in psychiatry. This could be achieved by involving relevant actors—such as researchers, health professionals, carers, but especially patients and service users—in the attempt to understand how individuals who (may) suffer from psychosis are rendered vulnerable in research and in clinical care. Empirical bioethics could constitute an appropriate methodology to develop a participatory account of vulnerability in psychiatry. Again, as a methodological suggestion, I argue that future research could address more closely the issue of the *value* of qualitative research for bioethics and of descriptive ethics for empirical bioethics.

Third, if having access to neurobiological information profoundly affects how those who (may) suffer from psychosis construct their identity, then ethical guidance is needed on how neurobiological information is to be acquired and delivered in the context of psychosis. Not only should future research provide that

guidance but also, more generally, bioethics should reflect on *narrative identity*. Not only should future research be concerned with the meaning of personal identity but also with how present and future individuals construct their narrative identity—in other words, with how they understand themselves. Bioethics research should address narrative identity in order to ensure the ethical translation of neuroscience and genomics into mental health. In doing so, future research should investigate not only the value of life but also *the life of values*.

Fourth, we must work towards developing an appropriate *theory of care* in psychiatry. A theory of care in psychiatry should recognise the (epistemic) value of carers' moral outlook in identifying, and responding to, the ethical challenges of technological convergence. To do so, this theory of care could be grounded in the ethics of care. This theory of care could thus address the question of *how* medical ethics can be a facilitator, and not a barrier, to scientific development and medical innovation in psychiatry.

Fifth, as machine learning and artificial intelligence increase their presence in medicine and in our lives, future research should investigate the challenges that they pose to our legal systems. These challenges will certainly include, but they will not be limited to, privacy and data management. With regard to psychiatry, legal theory will need to investigate the impact that machine learning and artificial intelligence might have on mental health research and on psychiatric care, within and *beyond* the issues of risk, harm, and coercion.

6.11 Concluding remarks

> The recruit comes into the establishment with a conception of himself made possible by certain stable social arrangements in his home world. Upon entrance, he is immediately stripped of the support provided by these arrangements. In the accurate language of some of our oldest total institutions, he begins a series of abasements, degradations, humiliations, and profanations of self. His self is systematically, if often unintentionally, mortified. He begins some radical shifts in his *moral career*, a career composed of the progressive changes that occur in the beliefs that he has concerning himself and significant others.[40]

Moral theory is concerned with the obligations we have towards each other. Deontological theories contend that these obligations arise from certain rules that we ought to follow. Consequentialist theories affirm that what is morally relevant are the consequences of our actions, and that obligations arise from the attempt to maximise the good consequences of our actions. Virtue ethics, care ethics, and other philosophical theories provide different accounts of moral obligations and of how they can be theoretically justified. Bioethics is concerned with the obligations we have towards each other in response to technological development and to advances in biomedicine. The kind of obligations that we investigate in bioethics pertain to present and future persons. We have obligations towards existing persons, and we *may* have specific obligations towards future generations. Do we also have obligations towards *past* generations? Can we have moral obligations towards those who have already lived and died? In one sense, I do not think we can. Those who have died have little to benefit from our actions. In another sense, I think we do. We may have a moral obligation to respect those who have died and to learn from their experiences, if their experiences have something important to teach us regarding morality.

The history of psychiatry is the laudable history of the many attempts to identify, diagnose, and treat mental illness. As such, it is the history of the many

[40] Goffman, *op. cit.*, 24.

attempts to treat, benefit, and ultimately to take care of those who suffer from mental illness. At the same time, the history of psychiatry is outrageous. It is the history of the 'great confinement'.[41] It is the story of how we came to confine those who suffered from mental illness—or were claimed to be so—in total psychiatric institutions.[42] Not only is it the story of how the mentally ill were deprived of their liberty often for the entire duration of their lives, but also of how they were stripped of their selves. Beyond that, the history of psychiatry is the story of how we came to accept coercion as part of our legal systems. Whether coercion may be considered outrageous is subject to debate. What is beyond debate is that coercing someone into being admitted to hospital when she does not wish so, or imposing treatment to someone when this is *against her will* are morally powerful acts.[43] Suffering from mental illness is one of the few reasons—if not the only reason—why most of our societies allow that. If there is any obligation we have towards those who have lived and died that can be inferred from the history of psychiatry, this is an obligation we have towards those who were institutionalised over its history: the obligation to learn the moral lessons that their lives can teach us.

The history of psychiatry reminds us that we must evaluate *carefully* how research on mental illness is conducted, how psychiatric treatment and care are delivered, and how mental health legislation shapes our social interactions. It reminds us that innovation in psychiatry does not happen in an ethico-legal vacuum. The debate between those who claim that mental illness is rooted in our biological structures and those who claim that mental illness is the result of psychosocial interactions and of the power imbalances that characterise our societies is far from over. It may be that the truth is situated somewhere between these two extremes. In this thesis, I have decided not to side with any of the two parties. I did this because I believed that being positioned somewhere in the middle of this debate would allow me, as an ethicist, to better evaluate the clinical, ethical, and social implications of recent advances in neurobiological approaches to psychosis. Yet, this debate prompts us to consider how psychiatry—and perhaps medicine as a whole—is *not*

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[41] Foucault, Michel, *Madness and Civilization. A History of Insanity in the Age of Reason* (London & New York: Routledge, 2001/1964), 35-60.
[42] Goffman, *op. cit.*
[43] Anonymous, 'What it feels like to be compulsorily detained for treatment', *The BMJ* 358 (2017): j3546.

morally neutral. Not only is psychiatry a clinical speciality but also a social activity and, as such, it is subject to ethico-legal scrutiny.

Clinical neurosciences are reshaping our understanding of the brain processes behind psychosis. Psychiatric genomics is reshaping our understanding of the molecular processes behind psychotic disorders, their inheritability, and our susceptibility to developing psychotic illness. More importantly, the convergence of neuroscience and genomics is reshaping our understanding of the neurobiology of psychosis. We can recognise that biomedical innovation and technological convergence have the potential to *transform* the way in which we understand and treat mental illness. At the same time, we must also recognise that this transformation will *not* be morally neutral. It will not be morally neutral because neuroscience and genomics, as scientific activities, are not morally neutral; because psychiatry, as a clinical and social activity, is not morally neutral. More importantly, this transformation will not be morally neutral because technological innovation might not be morally neutral.

In a sense, bioethics is based on the assumption that technology is *not* morally neutral. With this statement, I mean that technology is shaped by, and in turn shapes our individual and collective action. Technology "touches on almost everything vital to man's existence—material, mental, and spiritual."[44] It is a commitment of bioethics to try to unfold the moral significance of technological innovation in biomedicine. In this sense, bioethics aims *not* at rejecting technology *but* at questioning its moral significance and at guiding its impact over our lives. The contribution that bioethics can offer to the ethics of psychiatry is precisely to question the moral implications of technological innovation in mental health, and to provide avenues to ensure that the development of novel technologies respects the value we attribute to our lives.

In this thesis, I have investigated the ethical challenges that arise from the attempt of neuroscience and genomics to unveil the neurobiology of psychosis. I have explored some of the moral obligations we have towards each other with reference to this endeavour. I have argued that increased technological convergence

[44] Jonas, Hans, 'Toward a philosophy of technology', *Hastings Center Report* 9 (1) (1979): 34-43: 34.

requires improved interdisciplinary collaboration. Bioethics was born to strive for interdisciplinary collaboration between the biomedical sciences and the humanities. In a time where technologies merge faster than we can grasp, where data revealing information about our bodies, our minds, and our lives are collected, stored, and shared with countless means at countless times, where digital technologies and artificial intelligence are reshaping our reality, I believe that we need *meaningful* interdisciplinary collaboration more than ever. In this thesis, I have argued that such interdisciplinary collaboration should question and guide the use of new technologies in the present and in the future of psychiatry. I have argued that we need appropriate philosophical concepts to guide, and to emerge from, this interdisciplinary discussion. I have argued that we have both ethical and epistemic reasons to include not only philosophers, legal scholars, and scientists, but also health professionals, carers, and patients in the interdisciplinary discourse around technological innovation in psychiatry. Hence, I have supported the view that, if we are to include social actors in bioethical inquiry, we must do so with appropriate methodologies and with an eye at considering whether participatory research might provide insights that traditional research cannot provide. I have argued that we must consider whether our findings question the *political* structure of our societies and the *legal* systems that stem from it. Along with our obligation to investigate the impact of technology on society, we have an obligation to question—and if necessary, to amend—the ways in which our legal systems regulate our social interactions.

Overall, in this thesis I have argued that we ought to work towards a deeper and more nuanced understanding of the ethical implications of technological innovation in psychiatry. This involves questioning the structure of psychiatry, the nature of bioethics, and the role of technology in our lives. Novel technologies may create new opportunities as well as new problems. They may solve old problems or exacerbate them under a new guise. While it is legitimate to welcome the new opportunities brought about by technology, we must reflect on the old and the new problems created by technology in order to provide revised, meaningful, and appropriate solutions to them.

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APPENDIX A | Article two: Interview guides

Group A: Researchers

Themes	Questions
Warm up	- For how long have you been working as a researcher in psychology / psychiatry / mental health? - In few words, how would you describe your main research field? - Over the course of you career, have you been performing clinical research on psychotic disorders? What kind of research have you performed?
	In recent years, the development of medical technologies such as neuroimaging and whole genome sequencing has resulted in an increased interest in the neurobiology of psychosis and schizophrenia. As we know, psychotic disorders are best understood in a *bio-psycho-social* model, as they involve at the same time biological, psychological, and social factors.
	- Overall, what are your thoughts on the increased research interest in the neurobiology of psychotic disorders? - What do you feel could be the arguments for justifying conducting this kind of research?
Ethical issues: Clinical research	Some ethical and legal issues that may occur while performing *neuroscience* and *genomic* research with clinical populations have been identified. I would like to know your opinion on those.

- What are your thoughts on returning results from neuroimaging and genomic studies to research participants with a psychotic disorder?
- Would you consider it *beneficial* to return results to a clinical population with a psychotic disorder? Why / Why not?

- How would you behave if significant Incidental Findings (IFs) on a participant resulted from your research? Has this happened to you before? How have you reacted?
- Neuroimaging studies can incidentally highlight underlying brain conditions. Would you communicate these to participants? In what circumstances? How?
- Would you involve family members / carers / significant others?
- Genomic studies can generate IFs that can be relevant to family members, especially regarding the risk of developing specific conditions. What are your thoughts on this?

- One of the strongest ethical concerns about research into the neurobiology of mental illness is the lack of immediate Clinical Utility (CU). What are your thoughts on this?
- Do you think that neuroimaging or genomics could support diagnosis / prognosis / treatment of psychotic disorders? Why / Why not? How long will it take before we see CU in your estimation?
- Given the lack of immediate CU, do you feel that research into the neurobiology of mental illness is ethically justified? Why / Why not?
- How would you communicate lack of immediate CU to participants / family members?

- Genomics research aims to uncover the biological basis of vulnerability to psychosis, as well as familial risk. What are your thoughts on this? What about clinical utility?
- In your opinion, what are the ethical challenges of involving patients / service users with psychosis or schizophrenia in genomics research? You can mention as many as you want.
- What about young patients / service users or minors?
- Do you think that risk assessment based on genetic measures may be *beneficial* to individuals at high-risk or ultra-high-risk of developing a psychotic disorder? Why / why not?
- What are your thoughts on recent findings in GWAS studies on psychotic disorders and schizophrenia?

- What do you think would be the reasons to perform WGS / WES with patients / service users with a psychotic disorder?
- Do you see any ethical concern *not to* perform that?
- What do you think may be the ethical implications?
- What do you think would be the implications for patients / family members?

Ethical issues: Common

Genetic essentialism is defined as a tendency, in the general population, to identify biogenetic explanations of illness as the *only* possible explanations of a particular disorder, and genetic susceptibility / risk as genetic *inevitability* to develop the disorder.

- Do you think that genomic studies on mental illness may / may not contribute to enforce this tendency? Why / why not?
- Have you encountered this facet in your professional experience?
- Would you say that the clinical populations you work with are / are not prone to genetic essentialism?

- What about young / minor populations?
- How could researchers contribute to contrast genetic essentialism?

Likewise, neuro-essentialism is defined as the same tendency, with regard to neuroscientific studies on the neurological correlates of mental illness.

- Do you think that neuroscientific studies on mental illness may / may not contribute to enforce this tendency? Why / why not?
- Have you encountered this facet in your professional experience?
- Would you say that the clinical populations you work with are / are not prone to neuro-essentialism?
- What about young / minor populations?
- How could researchers contribute to contrast neuro-essentialism?

- How do you think that neuroscientific and genomic explanations of mental illness might affect individuals' vulnerability?
- What about young clinical populations?
- What about young individuals / minors in the prodromal phase of psychosis? What about their families and carers?

- In the case of young individuals / minors, how do you think that neurobiological measures would affect identity formation?
- What about early internalisation of genetic and neuro-essentialism?
- What about family interactions?

- Do you think that neurobiological explanations of mental illness may increase / decrease stigma and labelling at a social level?
- At the individual level?
- Do you see labelling that may derive from neurobiological diagnostic measures as beneficial / non-beneficial to patients / service users? Why?
- Do you think that neurobiological diagnostic measures would increase / decrease self-stigmatisation? Why / why not?

- Could you think of any ethical or legal issue that might derive from the introduction of neurobiological diagnostic / prognostic measures to informed consent procedures?

  You can refer to clinical research or clinical practice.

- Would you see any major ethical or legal issue arising from the use of neuroimaging or genomics measures in forensic psychiatry?

Potential clinical translation & ethical issues involved

Current translational efforts include: 1) neurobiological markers of vulnerability to psychosis / transition / disease progression; 2) neuro-functional markers in the psychosis prodrome; 3) drug discovery and development; 4) integration of different modalities with machine learning methods for individual prediction of psychosis transition.

- What are your thoughts on the potential clinical utility of the above translational efforts?
- Can you think of any ethical concerns that could arise from those?

- How do you think measures such as the ones described above may affect patients / service users' sense of identity?
- What about agency or personal autonomy?
- What about the risks of stigmatisation and labelling?

Impact on mental health care

- Given the current strong focus on early intervention for psychosis and schizophrenia in mental health services, do you think that the introduction of such measures could affect patients' clinical outcomes? Why / why not?
- What about patients / service users' engagement with EIS or other community clinical teams?
- What about patients being hosted in inpatient units?
- What about young / minor service users, and their families?
- What about mental health care providers, such as psychologists, psychiatrists, and social workers? How do you think they would welcome the potential introduction of such measures? Why?

Group B: Mental health professionals

Themes	Questions
Warm up	- For how long have you been working as a health care professional in mental health? - In few words, how would you describe your background and your current occupation? - Over the course of you career, have you been working alongside patients / service users with a psychotic disorder or schizophrenia? Can you give me some examples of your involvement with this population?
	In recent years, the development of medical technologies such as neuroimaging and whole genome sequencing has resulted in an increased interest in the neurobiology of psychosis and schizophrenia. As we know, psychotic disorders are best understood in a *bio-psycho-social* model, as they involve at the same time biological, psychological, and social factors. - Overall, what are your thoughts on the increased research interest in the neurobiology of psychotic disorders? - What do you feel could be the arguments for justifying conducting this kind of research?
Ethical issues: Common	Some ethical issues that may be identified while conducting neuroscience and genomic research with clinical populations can also be encountered in clinical practice. I would like to know your opinion on those. Genetic essentialism is defined as a tendency, in the general population, to identify biogenetic explanations of illness as the *only* possible explanations of a particular disorder, and genetic

susceptibility / risk as genetic *inevitability* to develop the disorder.

- Do you think that genomic studies on mental illness may / may not contribute to enforce this tendency? Why / why not?
- Have you encountered this facet in your professional experience?
- Would you say that the clinical populations you work with are / are not prone to genetic essentialism?
- What about adolescent / child populations?
- How could clinicians contribute to resist or combat genetic essentialism?

Likewise, neuro-essentialism is defined as the same tendency, with regard to neuroscientific studies on the neurological correlates of mental illness.

- Do you think that neuroscientific studies on mental illness may / may not contribute to enforce this tendency? Why / why not?
- Have you encountered this facet in your professional experience?
- Would you say that the clinical populations you work with are / are not prone to neuro-essentialism?
- What about adolescent / child populations?
- How could clinicians contribute to resist or combat neuro-essentialism?

- How do you think that neuroscientific and genomic explanations of mental illness might affect individuals' vulnerability?
- What about young clinical populations?

- What about young individuals / minors in the prodromal phase of psychosis? What about their families and carers?

- In the case of young individuals / minors, how do you think that neurobiological measures would affect identity formation?
- What about early internalisation of genetic and neuro-essentialism?
- What about family interactions?

- Do you think that neurobiological explanations of mental illness may increase / decrease stigma and labelling at a social level?
- At the individual level?
- Do you see labelling that may derive from neurobiological diagnostic measures as beneficial / non-beneficial to patients / service users? Why?
- Do you think that neurobiological diagnostic measures would increase / decrease self-stigmatisation? Why / why not?

- Could you think of any ethical or legal issue that might derive from the introduction of neurobiological diagnostic / prognostic measures to informed consent procedures?

  You can refer to clinical research or clinical practice.

- Would you see any major ethical or legal issue arising from the use of neuroimaging or genomics measures in forensic psychiatry?

Potential clinical translation & ethical issues involved	Current translational efforts of research findings include the following: 1) neurobiological markers of vulnerability to psychosis / transition / disease progression; 2) neuro-functional markers in the psychosis prodrome; 3) drug discovery and development; 4) integration of different modalities with machine learning methods for individual prediction of psychosis transition. - What are your thoughts on the potential clinical utility of the above translational efforts? - Can you think of any ethical concerns that could arise from those? - How do you think measures such as the ones described above may affect patients / service users' sense of identity? - What about agency or personal autonomy? - What about the risks of stigmatisation and labelling?
Ethical issues: Clinical practice	- In your opinion, is there any risk of increasing patients / service users' self-stigmatising attitudes by implementing novel neurobiological approaches to psychotic disorders? Why / why not? - How do you think that the introduction of measures such as the ones described before would affect your relationship with patients / service users? - In your opinion, would that improve / obstacle engagement? Why? - Would that affect in any way the relation of trust that you establish with patients / service users? Why / why not? - If accurate neurobiological measures for risk prediction (for developing psychosis or schizophrenia) were available, would you be willing to use them / propose them to patients / service users? Why / why not?

- How would you communicate the risk of developing a psychotic disorder based on neurobiological measures to patients / service users? What about the family / relevant others?
- Would you involve families in communicating the risk of developing a psychotic disorder or schizophrenia? Why / why not?
- What about over-diagnosis? In your opinion, could there be a risk of over-diagnosis of psychotic disorders, should neurobiological measures of risk prediction be implemented? Why / why not?
- To what extent would you, as a mental health professional, rely on those measures?
- In the case of scarcity of resources, on what basis would you allocate them? Following which criteria?

- In your opinion, what would be the impact on patients / service users' families and carers?
- What about the young / prodromal population? What about minors?
- What about the families / relevant others of chronic patients with a psychotic disorder or schizophrenia?

Genetic Testing (GT) is not currently available for common complex mental disorders such as schizophrenia. Given that psychotic disorders involve at the same time biological, psychological, and social factors, some people argue that it will *never* be available, or that it *should not* available.

- What are your thoughts on this matter? Remember, you can be as honest as you want.

	- If GT were available for psychotic disorders, would you be willing to use it / propose it to patients / service users? Why / why not? - Would you consider offering genetic counselling? Why / why not? - What impact do you think GT for psychotic disorders could have on patients / services users? - What about the young population? What about minors? - What impact do you think GT for psychotic disorders could have on individuals already identified as at-risk, based on clinical presentation of prodromal symptoms, or on family history? - What impact do you think GT for psychotic disorders could have on their families / relatives? - Should GT be available for psychotic disorders, would you foresee any risks of genetic discrimination based on the results of such tests? - Why / why not? - How would you communicate the results of such tests to patients / services users? And to their families / relevant others?
Impact on mental health care	- Given the current strong focus on early intervention for psychosis and schizophrenia in mental health services, do you think that the introduction of neurobiological measures could affect patients' clinical outcomes? Why / why not? - What about patients / service users' engagement with EIS or other community clinical teams? - What about patients being host in inpatient units? - What about young / minor service users, and their families? - What about mental health care providers, such as psychologists, psychiatrists, and social workers? How do

you think they would welcome the potential introduction of such measures? Why?

APPENDIX B | Article two: Coding manuals

Group A: Researchers

Bold = code / theme; *Italic = code description*

ARGUMENTS FOR / AGAINST RESEARCH:

Pro:	*Arguments in favour of conducting clinical research on the neurobiological (neuroscience and genomics) correlates of psychosis and schizophrenia.*		
	Legitimate area of inquiry:	*Neuroscience and genomics of psychotic illness are legitimate areas of scientific inquiry, as much as psychosocial research / interventions.*	
		Informed consent and autonomy argument:	*No reason to believe that an individual with psychosis, but who has capacity, should be given special consideration.*
	Knowledge good in itself:	*Scientific knowledge has value in itself and does not need justification.*	
	Duty towards society:	*Scientists have a moral duty towards society to investigate the neurobiological basis of mental illness.*	
	Better diagnosis / Novel treatment:	*Neuroscience and genomics have the potential to produce novel treatments / medications for psychotic disorders.*	
Against:	*Arguments against conducting clinical research on the neurobiological (neuroscience and genomics) correlates of psychosis and schizophrenia.*		
	Resources:	*Resources for mental health research / care are scarce.*	
		High cost:	*Neurobiological research has high costs.*
		Drains funding:	*Neurobiological research drains funding from other types of research.*

No novelty, just new technologies:	*Neurobiological research is not new. It has been ongoing for decades, and has produced little clinically useful knowledge. What is new is the technology.*
Psychosocial research has greater therapeutic impact:	*Research on psychosocial factors / interventions has proven to have greater therapeutic impact.*
Potential for harmful developments:	*Neurobiological research has the potential to promote harmful future developments in psychiatry. There are potentially harmful driving forces in psychiatry.*

RETURNING RESULTS:

Context-dependent:	*Returning results to research participant is dependent upon the context of the research (methodology, results) and populations / individuals.*	
	Consider risks / situation:	*Researchers must consider the risks / situation for research participants.*
	Tailor communication with participants:	*Communication of research results must be tailored to the situation / capacity / understanding of participants.*
Participants' capacity:	*If participants are deemed to have capacity to take part in research, they should be offered the possibility to know the results. Anti-discriminatory argument.*	
Genomics: more sensitive area:	*Genomic research deals with more sensitive information and research procedures. Careful consideration should be given on whether / how to return results.*	
	Managing genetic information:	*Handling / managing genomic information is more complex than neuroscientific information.*
	Risk of deterministic thinking:	*There is a risk to promote deterministic think (e.g. genetic predisposition as 'fate', 'destiny').*
	Discrimination / Insurances:	*Genetic information may have impact on health insurance policies (e.g. US health care model).*

INCIDENTAL FINDINGS:

Participant's capacity:	*Disclosure of incidental findings to a participant should be considered if the participant has capacity.*	
Duty to report / right (not) to know:	*Researchers have a moral duty to report (clinically) relevant incidental findings. Participants retain a right (not) to know incidental findings.*	
Shared decision making:	*Disclosure of incidental findings must be considered through a shared decision-making process involving several actors.*	
	Other professionals:	*Involve other professionals (GP, psychiatrist, colleagues) in the decision-making process.*
	Family:	*Consider involving the participant's family in the decision-making process.*
		Always consult family for minors: *The family should always be consulted in case of minors.*
Refer to protocol / guidelines:	*Most of the ethico-legal dilemmas related to disclosure of incidental findings can / must be resolved by referring to the research protocol and / or established guidelines.*	
Avoid therapeutic misconception:	*In considering / disclosing incidental findings, researchers must be aware of the risk that participants might see the researcher as having a clinical, rather than a research role.*	

LACK OF CLINICAL UTILITY (CU):

Ways to respond to / communicate lack of CU:	*Ways to conceptualise and justify the lack of immediate clinical utility of neurobiological research. Ways to communicate this lack of CU to research participants.*	
	Intrinsic value of science:	*Science and knowledge production have intrinsic value.*
	Honesty & transparency:	*Researchers must be honest and transparent regarding lack of CU.*
	Good communication with participants:	*Researchers must establish good communication with participants, so that they can communicate the lack of CU.*

Genomics has less potential CU:	*Genomic science has had, and still has less potential clinical utility if compared with other areas of clinical research.*	
	Molecular genomics has greater potential:	*Novel molecular genomics, including WGS has greater potential CU than traditional genomics.*
Hope for benefits in the future:	*Lack of immediate CU is balanced by the hope for potential future clinical benefits, which may derive from current research.*	
Psychosocial approaches have greater CU:	*Psychosocial research has had and still has more clinical utility.*	

ESSENTIALIST THINKING (ET):

Clients vs. professionals:	*Clients (e.g. service users, patients, research participants) and professionals (clinicians and researchers) hold different views regarding mental illness.*		
	ET more common in professionals:	*ET is more common in professionals (with a neurobiological background) rather than in clients.*	
	ET less common in clients:	*ET is generally not common in clients (psychosocial explanations of mental illness are more common).*	
		Great variation in clients:	*Clients show a great variety of visions regarding the origin / causes / nature of mental illness.*
Genomics:	*Genomics and ET.*		
	Increase ET:	*Genomic science may increase ET. Genes as 'destiny', 'fate'. Historical implications of genomic science for mental illness.*	
	Reduce ET:	*Development of genomic science may reduce ET.*	
		Complex conditions:	*Molecular genomics reveals that psychotic illness is complex, non-mendelian.*

			Other risk factors:	*Molecular genomics reveals that genetic predisposition interacts with other risk factors (e.g. gene-environment interaction).*
Neuroscience:	*Neuroscience and ET.*			
	Increase ET:	*Neuroscience may increase ET (e.g. psychosis and schizophrenia understood as pure brain disorders).*		
			Broken brain model:	*Neuroscientific findings may boost the idea of mental illness due to a 'broken brain'. This may increase ET.*
			Over-represented by media:	*Neuroscientific findings are over-represented in the media, if compared with psychosocial approaches. This may increase ET.*
			Positive effects of ET:	*ET may have positive effects on the way individuals frame their responsibility towards their acts and illness.*
	Reduce ET:	*Better understanding of neurobiological 'correlates' of mental illness could reduce ET.*		
Ways to contrast ET:	*Ways in which researchers could contribute to contrast ET.*			
	Educating the public:	*Researchers should have a role in educating the public about the real implications of the neurosciences of mental illness.*		
	Better dissemination / communication:	*Researchers should promote clearer dissemination of research findings and better communication with the media.*		
			Biological 'factors', not 'causes':	*Researchers should educate the public about the fact that biological 'factors' are not direct / only 'causes' of mental illness.*

IMPACT:

On self:	*Neurobiological explanations of psychotic illness have an impact on self / identity.*	
	Illness rejection & externalisation:	*Mental illness viewed as something 'external' to self (e.g. brain disorder / chemical imbalance) and thus: 1) rejected, or 2) externalised. Positive and negative consequences.*
	Illness integration:	*Mental illness viewed as something part of self (e.g. my brain, my genes, my biology), and thus integrated within the identity. Mostly positive consequences.*
		Promote resilience: *Illness integration promotes resilience (e.g. learning how to accept symptoms, how to deal with symptoms, instead of aiming for full remission).*
	Risk of hopelessness:	*Neurobiological explanations of mental illness may promote hopelessness in clients (e.g. psychosis as permanent, chronic condition).*
On families:	*Neurobiological explanations of psychotic illness impact on families of (young) people.*	
	Risk of paternalistic role:	*Within a biomedical model of psychotic illness, families may tend to 'control' a young person with psychosis, and assume a paternalistic role.*
On life choices:	*A neurobiological understanding of psychotic illness may impact on individual's life choices, in a positive way (avoid exposing oneself to risk factors, e.g. cannabis), or negative way (avoid pursuing certain life choices, e.g. education).*	
	Reproductive choices:	*A neurobiological understanding of psychotic illness may impact on an individual's reproductive choices (e.g. wish not to pass this condition to one's offspring).*

STIGMA & LABELLING:

Psychosocial models:	*Impact of psychosocial models of psychotic illness on social stigma and labelling.*

	De-stigmatising:	*Psychosocial models decrease social stigma.*	
		Blame social factors:	*Psychosocial models of psychotic illness reduce self-blame, as they focus on social risk factors.*
		Promote hope and empowerment:	*Psychosocial models of psychotic illness promote hope towards recovery, and promote individual empowerment.*
Neurobiology:	*Impact of neurobiological models of psychotic illness on social stigma and labelling.*		
	Stigmatising:	*Neurobiological models increase social stigma.*	
		Broken brain model:	*The 'broken brain' model creates a category of 'different / diverse' individuals.*
		Reduced potential for recovery:	*A neurobiological understanding of psychotic illness reduces the potential for recovery (permanent, chronic condition).*
	De-stigmatising:	*Neurobiological models decrease social stigma.*	
		Illness removes responsibility:	*Psychotic individuals are not 'responsible' for their illness / condition.*
		Illness impairs agency:	*Psychotic individuals are not always / fully in control of their actions, therefore they are not to blame / stigmatise.*
		More accurate diagnosis:	*More accurate diagnostic procedures based on neurobiology reduce stigma.*

		Better understanding of illness:	*Better understanding of the condition (as a medical disorder) removes stigma (e.g. AIDS, cancer, dementia).*

CLINICAL TRANSLATION:

Potential benefits:	*Translating findings from neuroscience and genomics into clinical care may produce potential benefits.*		
	Prevention:	*Neuroscience and molecular genomics may positively impact on prevention of psychosis and schizophrenia (e.g. by identifying at-risk populations).*	
	Change diagnostic system:	*Neuroscience and molecular genomics may radically change our (already broken) diagnostic system.*	
	Better treatment / medications:	*Neuroscience and molecular genomics will produce novel and better treatments / medications for psychosis and schizophrenia.*	
No impact:	*Neuroscience and genomics will have no substantial impact on how clinical care is delivered.*		
Potential harms:	*Translating findings from neuroscience and genomics into clinical care may result in risk of harm for (young) clinical populations.*		
	Risk of over-diagnosis / overtreatment:	*Using neuroscience and genomics in clinical care increases the risk of over-diagnosing and thus over-treating young (healthy) individuals.*	
	Scarce resources:	*Resources for mental health care are already scarce.*	
		Impact on existing resources:	*Novel biomedical technologies may impact on current resource allocation.*
		No money for new technologies:	*Mental health care shows a structural scarcity of resources to support (fair) access to new technologies.*
Impact on services:	*Impact on current mental health services.*		

	Possible professional conflict:	*Different professionals will probably react in very different ways, thus possibly generating moral / ethical conflicts.*	
	Clinicians' response:	*Reaction of mental health professionals to the introduction of neuroscience / genomic based diagnosis / treatment.*	
		Based on their background:	*Clinicians' reaction may be affected by their professional background.*
		Scepticism:	*Most mental healthcare providers may be sceptical of the clinical utility of translational efforts.*

Group B: Mental health professionals

Bold = code / theme; *Italic = code description*

ARGUMENTS FOR / AGAINST RESEARCH:

Pro:	*Arguments in favour of conducting clinical research on the neurobiological (neuroscience and genomics) correlates of psychosis and schizophrenia.*		
	Legitimate area of inquiry:	*Neuroscience and genomics of psychotic illness are legitimate areas of scientific inquiry, as much as psychosocial research / interventions.*	
		Informed consent and autonomy argument:	*No reason to believe that an individual with psychosis, who has capacity, should be given special consideration. No discrimination argument.*
	Knowledge good in itself:	*Scientific knowledge has value in itself and does not need justification.*	
	Better understanding of illness:	*Neurobiological research is essential to reach a better understanding of psychotic illness.*	
	Better diagnosis / Novel treatments:	*Neuroscience and genomics have the potential to produce novel treatments / medications for psychotic disorders.*	
Against:	*Arguments against conducting clinical research on the neurobiological (neuroscience and genomics) correlates of psychosis and schizophrenia.*		
	Drains funding:	*Neurobiological research drains funding from other types of research.*	
	Potential for harmful developments:	*Neurobiological research has the potential to promote harmful future developments in psychiatry. There are potentially harmful driving forces in psychiatry.*	
		Negative impact on clients:	*Neuroscience and genomics could have a negative impact on clients' self.*
	Lack of CU:	*Neurobiological research has traditionally produced few useful treatments / interventions.*	

	Psychosocial research has greater CU:	*Research on psychosocial factors / interventions has proven to have greater therapeutic impact.*	

ESSENTIALIST THINKING:

Great variation in clients:	*Clients show a great variety of visions regarding the origin / causes / nature of mental illness.*		
	Clinicians' responsibility in shaping views:	*Clinicians hold great responsibility in shaping patients and service users' views on the nature of their mental illness.*	
Genomics:	*Genomics and ET.*		
	Increase ET:	*Genomic science may increase ET. Genes as 'destiny', 'fate'. Historical implications of genomic science for mental illness.*	
		Fatalistic approach / Inevitability:	*Genomic science may instil a fatalistic approach toward illness = illness as inevitable.*
		Risk of hopelessness:	*Genomic science may instil loss of hope towards recovery.*
Neuroscience:	*Neuroscience and ET.*		
	Increase ET:	*Neuroscience may increase ET (e.g. psychosis and schizophrenia understood as pure brain disorders).*	
		Deterministic / medical approach:	*Neuroscience could boost a deterministic medical approach to psychosis, which does not consider social and psychological factors.*
	Reduce ET:	*Better understanding of neurobiological 'correlates' of mental illness could reduce ET.*	
Ways to contrast ET:	*Ways in which mental health professionals could contribute to contrast ET.*		

	Refer to clinical guidelines / evidence:	*Mental health professionals should refer to the latest clinical guidelines / latest scientific evidence in shaping their practice.*
	Effective / communication:	*Mental health professionals should foster good communication with clients on the significance and implications of neurobiology.*
	Promote hope and optimism:	*Mental health professionals should promote hope and instil a sense of optimism in clients.*

IMPACT:

On self:	*Neurobiological explanations of psychotic illness have an impact on self / identity.*		
	Illness integration:	*Mental illness viewed as something part of self (e.g. my brain, my genes, my biology), and thus integrated within the identity. Mostly positive consequences.*	
		Promote resilience:	*Illness integration promotes resilience (e.g. learning how to accept symptoms, how to deal with symptoms, instead of aiming for full remission).*
	Undermine agency and recovery:	*Neurobiological explanations of psychotic illness may undermine the sense of agency of clients, and their perceived potential for recovery.*	
On families:	*Neurobiological explanations of psychotic illness impact on families of (young) people.*		
	Risk of family conflict / distress:	*Neurobiological explanations of psychotic illness may generate conflicts and distress within the family (blame, guilt, and distress).*	
	Risk of paternalistic role:	*Within a biomedical model of psychotic illness, families may tend to 'control' a young person with psychosis, and assume a paternalistic role.*	

On life choices:	*A neurobiological understanding of psychotic illness may impact on individual's life choices, in a positive way (avoid exposing oneself to risk factors, e.g. cannabis), or negative way (avoid pursuing certain life choices, e.g. education).*	
	Reproductive choices:	*A neurobiological understanding of psychotic illness may impact on an individual's reproductive choices (e.g. wish not to pass this condition to one's offspring).*

STIGMA:

Stigma social issue, not related to aetiology:	*Social stigma attached to mental illness is independent from theories about aetiology and causation. Stigma is primarily a social / cultural issues, it has nothing to do with aetiology and causation.*		
	Stigma attached to diagnosis:	*Social stigma arises from psychiatric labels / diagnoses rather than behaviour. Labels of 'schizophrenia' and 'psychosis' generate social stigma.*	
	Impact of media / cultural discourse on stigma:	*Media have a great impact on how stereotypes on mental illness are formed, and social stigma reproduced.*	
Neurobiology:	*Impact of neurobiological models of psychotic illness on social stigma and labelling.*		
	Stigmatising:	*Neurobiological models increase social stigma.*	
		Broken brain model:	*The 'broken brain' model creates a category of 'different / diverse' individuals.*
	De-stigmatising:	*Neurobiological models decrease social stigma.*	
		Illness removes responsibility:	*Psychotic individuals are not 'responsible' for their illness / condition, thus not to blame.*

		Labels may be useful in practice	*Diagnostic categories / labels may be useful for mental health professionals to direct clinical practice.*

CLINICAL TRANSLATION:

Potential benefits:	*Translating findings from neuroscience and genomics into clinical care may produce potential benefits.*		
	Prevention:	*Neuroscience and molecular genomics may positively impact on prevention of psychosis and schizophrenia (e.g. by identifying at-risk populations).*	
	More targeted referrals / treatments:	*Neuroscience and molecular genomics will produce novel and better treatments / medications for psychosis and schizophrenia.*	
Potential harms:	*Translating findings from neuroscience and genomics into clinical care may result in harm for (young) clinical populations.*		
	More invasive measures:	*Diagnostic measures based on neuroscience and genomics may be more 'invasive' than clinical interview / assessment.*	
		Risks for privacy & confidentiality:	*Using genomic / neuroscience in mental health may pose threats to clients' privacy and confidentiality.*
	How to use that information? / no viable options:	*Once information on genomic risk / biology of the brain is acquired, how to use that information in a clinically useful way? There may be no viable options.*	
		Risk of labelling:	*There is a risk that clinical translation will only result in additional labelling of clients.*
	Risk of hopelessness/ disengagement:	*Clinical measures based on neurobiology may perpetuate a sense of hopelessness and inevitability of psychotic illness. This could result in clients disengaging from services.*	

EFFECTS OF NOVEL DIAGNOSTIC TOOLS:

On client's self:	*Novel diagnostic tools based on neuroscience and genomics may have an impact on client's self /identity.*		
	Depends on how information is communicated:	*Impact on the identity of (young) clients will depend on how neurobiological information is communicated, and how it is used in the therapeutic relationship.*	
		Potentially harmful:	*There is a potential for harming clients' conception of self / identity if there is no appropriate communication.*
		Beneficial if effective communication:	*Information on neurobiology may be beneficial to clients if appropriate communication strategies are in place.*
On clinician-patient relationship:	*Novel diagnostic tools based on neuroscience and genomics may have an impact on clinician – patient relationship.*		
	Potential conflict on therapy:	*Using diagnostic tools based on neurobiology could generate tensions between professionals and clients on therapeutic options. Risk of 'moral coercion' towards therapeutic options.*	
	Psychosis risk communication:	*Moral challenges of communicating psychosis risk to help-seeking or asymptomatic individuals.*	
		Risk is not inevitability:	*Mental health professionals should communicate that psychosis risk is not inevitability to develop psychotic illness.*

		Psychosis very common in general population:	*Mental health professionals should communicate that psychosis is very common in the general population, and is not equal to psychotic illness.*
On practice:	*Novel diagnostic tools based on neuroscience and genomics may have an impact on clinical practice.*		
	Risk of medicalisation:	*There is risk to medicalise mental and behavioural difficulties.*	
	Risk of over-diagnosis:	*Using novel diagnostic tools based on neurobiology could result in over-diagnosing people.*	
		Over-diagnosis is already happening:	*Over-diagnosis of psychotic illness is already happening / is part of the history of psychiatry.*
		Neurobiology could reduce misdiagnosis:	*Diagnostic tools based on neurobiology could reduce misdiagnosis / wrong diagnosis of psychotic illness.*
On services:	*Novel diagnostic tools based on neuroscience and genomics may have an impact on how mental health services work.*		
	Possible professional conflict:	*Different professionals will probably react in very different ways, thus possibly generating moral / ethical conflicts.*	
	Clinicians' response:	*Reaction of mental health professionals to the introduction of neuroscience / genomic-based diagnosis / treatment.*	
		Scepticism:	*Most mental health care providers may be sceptical of the clinical utility of translational efforts.*

		Based on background:	*Clinicians' reaction may be affected by their professional background.*

GENETIC TESTING:

Impact:	*(Hypothetical) genetic testing for predisposition to psychosis or schizophrenia may affect individuals.*		
	On at-risk individuals:	*Impact of GT on individuals already identified as being at-risk through clinical assessment.*	
		Affect views on treatability:	*GT could affect clients' views on treatability of psychotic illness (e.g. untreatable / fatalistic / useless talking therapies).*
		Remove control over illness:	*GT could instil a sense of lack of control over the illness / undermine potential for recovery.*
	On reproductive choices:	*GT may impact on an individual's reproductive choices (e.g. wish not to pass the condition to one's offspring).*	
	On families:	*GT may impact on family relationship.*	
		Blame and guilt:	*GT may generate feelings of blame and guilt for 'passing on the illness / being responsible for someone else's psychosis.'*
Harms:	*(Hypothetical) genetic testing for predisposition to psychosis or schizophrenia may generate potential harms.*		
	Risk of disengagement from services:	*Risk that clients disengage from mental health services after receiving information on genetic predisposition to psychotic illness.*	
	Risk of hopelessness / determinism:	*Risk to instil a sense of hopelessness towards recovery in clients / sense of determinism in developing psychotic illness.*	

	Risk of discrimination: Insurance / jobs:	*Risk of discrimination that could derive from holding genetic information on predisposition to psychosis and schizophrenia (e.g. insurance, job applications, benefit applications).*	
		Discrimination already present:	*Discrimination towards people with mental illness is already present, and it may be exacerbated by GT.*
		Risk of information leak (always on record):	*Risk of information leak with regard to predisposition to psychotic illness / risk that such information may always stay on a 'person's record'.*
Benefits:	*(Hypothetical) genetic testing for predisposition to psychosis or schizophrenia may generate potential benefits.*		
	Could have CU where there is a long family history of MI:	*GT for predisposition to psychosis or schizophrenia may be beneficial and support mental health professionals where there is long family history of mental illness. Clinical benefits could be gained through prevention and early intervention.*	

APPENDIX C | Article three: Focus group guide | Group C: Carers

Sessions	Questions
Warm up (20 mins)	Recent years have seen the development of novel medical technologies. These include neuroimaging (brief description) and genetic techniques. Researchers are currently trying to understand the biological processes related to psychotic experiences and schizophrenia. This does not mean that psychosis or schizophrenia are just biological conditions. As we know, psychotic disorders involve at the same time biological, psychological, and social factors [put emphasis]. However, a better understanding of the biological processes could help to provide better diagnosis, prognosis and treatment options to patients and service users. - How many of you are familiar with what I am describing? [show of hands]. - If people raise hands, inquire: In general, what are your thoughts about this approach to psychotic disorders? o *Possible probes*: - How do you understand psychosis / schizophrenia? - If you were to describe psychosis and schizophrenia to someone who does not know what it is, how would you describe it? - If people do not raise hands: o describe a bit more in depth neuroimaging and genomics o promote engagement with participants

- What do you feel could be the arguments for justifying conducting this kind of research?
    - *Possible probes*:
        - Help to understand the condition?
        - Help patients / service users to understand their experiences?
        - Identify an appropriate diagnosis?
        - Enable early detection?
        - Improve prognosis?
        - Improve clinical outcomes?
        - improve treatments available?

Focusing exercise: vignette (30 mins)

Now I would like us to do an exercise altogether. I will distribute a vignette, which describes an imaginary case scenario. I would like you to read the vignette, and then we will have a discussion and go through some questions together.

Please, remember that there are no right or wrong answers. Also, remember that you can feel free to say whatever you want.

- Distribute vignette
- Allow time for people to read the vignette (approx. 5 minutes)
- Open up and lead discussion (approx. 25 minutes)

[The case vignette has been inserted in the main text in section 4.3.3 so it is not reported here]

Exploration of common ethical issues (20 mins)

- How would you feel if there was a way to assess your risk of developing a psychotic disorder without you having any symptoms, just based on your family history and biological measures?
- Would you be interested in knowing that? Why / why not?
- Would you be interested in knowing for your children? Why / why not

Now I would like to explore with you some common ethical issues.

- What impact do you think that measures such as the ones we have described could have on the way patients / service users see themselves?
- What would be your reaction if a person you take care of were to have a brain scan or a blood test performed for assessing the risk of developing a psychotic disorder?
    - *Possible prompts*: interest? Curiosity? Fear? Anger?

We know that having a psychiatric diagnosis, or even attending a mental health service can generate social stigma towards patients and service users.

- Has anyone experienced social stigma towards the person you take care of? What was your reaction to that?
- Do you think that a stronger focus on the biological aspects of psychotic disorders would *increase* or *decrease* stigma? Why?

The implementation of neurobiological approaches to psychosis could result in improvements in formulating a diagnosis. Some people think this would result in *labelling*.

- Do you think that a diagnosis based also on biological factors would be beneficial to patients / service users? Why / why not?
- Do you think patients may understand this as if they have a 'brain condition'?
- Do you think that 'giving a name' to psychotic experiences can help people cope with their conditions? Why / why not?
- Do you think that this could lead to an increase in self-stigma in patients or service users? Why / why not?
- Do you think that having a more accurate name for a psychiatric condition may improve engagement with mental health services? Why / why not?
- What about compliance with medications? Why / why not?

- If you think back about what we have discussed, how do you think this could affect family life? Can anyone give me an example?
- How do you think this would affect your relationship with the person you take care of?

Questions from participants & closing (10 mins)

That was the last topic I wanted to discuss with you. If there is anything that was not covered during the focus group, and that you would like to discuss, please feel free to tell me.

Allow time to answer potential questions from FG participants

Thank participants for their participation in the study and for taking the time to answer all the questions. Briefly explain what will happen to data, and provide means to re-contact the research team.

APPENDIX D | Article three: Coding manual | Group C: Carers

Bold = code / theme; *Italic = code description*

ANGER:

Frustration:	*Carers' frustration towards their and their cared-for's condition.*	
	At medical profession:	*Frustration towards medical profession and mental health service provision.*
	At research:	*Frustration towards the ineffectiveness of medical research on psychosis / schizophrenia.*
	Lack of social support:	*Lack of social support for carers and for individuals suffering from psychosis.*
	Coercion and moral distress:	*Experiences of coercion / involuntary hospitalisation of cared-for and link with carers moral and psychological distress.*
	Expert role of carers:	*Carers' expertise in caring for a person with a psychotic disorder is essential and should be valued by medical profession.*
Stigma:	*Carers' experiences and conceptualisations of social stigma.*	
	Blame on parents for illness:	*Parents' blame and self-blame towards cared-for's mental illness.*
	Carers' shame / fear of social judgement:	*Carers' shame of their family situation and fear of social judgment.*
	Experiences of discrimination:	*Carers' and cared-for's experiences of discrimination due to mental illness.*
	Stigma and fear related to diagnosis:	*Social stigma and fear related to mental illness depend on labelling and are related to diagnosis.*

	Frustration at 'politically correct':	*Carers' frustration towards 'politically correct' initiatives / language to reduce stigma.*	
	Media as drive of social stigma:	*Media perceived as a main drive of social stigma around mental illness.*	
	Need for education on social stigma:	*It is necessary to educate the public around mental illness in order to tackle social stigma.*	
	Stigma and neurobiology:	*Connections between social stigma and neurobiological understandings of mental illness.*	
		Research in general can reduce stigma:	*Any improved understanding of the nature of mental illness can reduce social stigma.*
		Neurobiology could reduce stigma by removing blame:	*Neuroscience and genomics could remove responsibility towards mental illness, and thus reduce stigma.*
Understandings of illness:	*Carers' understandings of the nature and aetiology of psychosis.*		
	Psychosis is (not) an illness:	*Carers' ambivalence on the idea that psychosis is / is not a form of illness or a medical condition.*	
	Schizophrenia just a collection of symptoms:	*Schizophrenia does not exist as a discrete condition. It is only a collection of symptoms.*	
	Right understanding is biological / biopsychosocial:	*The correct model of psychosis is a biological model, or a model that takes into account the biological components of illness.*	
	Diagnostic system is flawed:	*The psychiatric diagnostic system does not reflect the reality of mental illness, it is a collection of arbitrary labels.*	

HOPES:

Need for effective intervention:	*Carers' need for effective interventions that can cure / increase the quality of life of their cared-for.*		
	Timely and accurate diagnosis:	*Timely and accurate diagnosis is essential to effective intervention and care.*	
	Effective medication:	*Need for more effective medication with less severe side effects.*	
		Medication is currently trial & error:	*Prescription of medication for psychosis is arbitrary and not targeted.*
		Neurobiology may support accurate prescription:	*A greater understanding of the neurobiology of psychosis could support accurate prescription.*
	Effective prevention:	*Effective prevention of psychosis and schizophrenia is essential.*	
		Prediction useful only if intervention available:	*Prediction of psychosis and schizophrenia is useful only if appropriate intervention is available.*
Strive for knowledge / understanding of illness:	*Carers' demand for an increased understanding of psychosis and psychotic disorders.*		
	Research has vital relevance:	*Any form of research on psychosis has vital relevance to support care.*	
	Fair access to research / treatment:	*Individuals who suffer from a psychotic disorder deserve better access to research and treatment (justice requirement).*	
	Peer-support groups are vital to carers:	*Peer-support groups are vital for the well-being of carers.*	

Communication:	*Need for effective communication carers / cared-for / medical profession.*	
	Detailed information on research to carers:	*Carers have a right be informed of relevant research opportunities for their cared-for.*
	Careful communication (on research) with participants:	*Careful communication with individuals with psychosis, both in research and care, is required from researchers and mental health professionals.*
	Confidentiality as a barrier:	*Confidentiality is a barrier to effective communication and effective care. Confidentiality is often used by professionals as a tool to exclude carers from information / treatment decisions.*
	Effective communication with mental health professionals:	*Effective communication between carers and mental health professionals is paramount to support patient care.*
Benefits of psychosis prediction / risk identification:	*Psychosis prediction and psychosis risk identification may produce clinical and personal benefits.*	
	Impact on patient's life choices:	*Psychosis prediction and risk identification could positively affect patients' life choices.*
	Extension of individual choices:	*Psychosis prediction and risk identification could extend the spectrum of life choices of people who (may) suffer from mental illness.*
	Increased hope towards recovery if effective intervention:	*Psychosis prediction and risk identification could increase hope towards recovery if effective intervention was available.*

FEARS:

Resources:	*Research and interventions must face a structural lack of resources in mental health services.*	
	No money for new technologies:	*There might be no money to implement new technologies in research and care.*
	Poor treatment has societal costs:	*Poor treatment of individuals who suffer from mental illness has great societal costs.*
Harms of psychosis prediction / risk identification:	*Psychosis prediction and psychosis risk identification may harm individuals.*	
	Prevention (prediction) of schizophrenia is not possible:	*Effective prevention or prediction of schizophrenia via neuro-technology or other methods is not possible.*
	Risk of medicalisation and over-diagnosis:	*Psychosis prediction and risk identification could exacerbate medicalisation of mental illness and result in over-diagnosis.*
	Burden on (young) individuals / iatrogenic effect:	*Psychosis prediction and risk identification could be psychologically and morally burdensome to (young) individuals. At worse, it could increase the likelihood to suffer from mental illness (iatrogenic effect).*
	Young people difficult to engage in research:	*Young people are difficult to engage in research on psychosis prediction / risk, mainly for fear or incapacity to appreciate the importance of research.*