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The benefit of foresight? An ethical evaluation of predictive testing for psychosis in clinical practice

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ABSTRACT

Risk prediction for psychosis has advanced to the stage at which it could feasibly become a clinical reality. Neuroimaging biomarkers play a central role in many risk prediction models. Using such models to predict the likelihood of transition to psychosis in individuals known to be at high risk has the potential to meaningfully improve outcomes, principally through facilitating early intervention. However, this compelling benefit must be evaluated in light of the broader ethical ramifications of this prospective development in clinical practice. This paper advances ethical discussion in the field in two ways: firstly, through in-depth consideration of the distinctive implications of the clinical application of predictive tools; and, secondly, by evaluating the manner in which newer predictive models incorporating neuroimaging alter the ethical landscape. We outline the current state of the science of predictive testing for psychosis, with a particular focus on emerging neuroimaging biomarkers. We then proceed to ethical analysis employing the four principles of biomedical ethics as a conceptual framework. We conclude with a call for scientific advancement to proceed in tandem with ethical consideration, informed by empirical study of the views of high risk individuals and their families. This collaborative approach will help ensure that predictive testing progresses in an ethically acceptable manner that minimizes potential adverse effects and maximizes meaningful benefits for those at high risk of psychosis.

1. Introduction

Risk prediction for psychosis has advanced to the stage at which it could feasibly become a clinical reality. Neuroimaging biomarkers play a central role in many risk prediction models. Using such models to predict the likelihood of transition to psychosis in individuals known to be at high risk has the potential to meaningfully improve outcomes, principally through facilitating early intervention (Correll et al., 2018). In addition, knowledge of risk status can enable individuals to minimize modifiable risk factors, better understand subthreshold psychotic experiences, access self-education and peer support, and make future plans in case of illness onset. In time, it may be possible to intervene to avert transition to psychosis, however, at present the evidence base for preventative interventions remains inconclusive (S Tognin et al., 2019). These potential gains are compelling; however they must be evaluated in light of the broader ethical ramifications of this prospective development in clinical practice. This paper advances ethical discussion in the field in two ways: firstly, through in-depth consideration of the distinctive implications of the clinical application of predictive tools; and, secondly, by evaluating the manner in which newer predictive models incorporating neuroimaging alter the ethical landscape. We initially outline the current state of the science of predictive testing for psychosis, with a particular focus on emerging neuroimaging biomarkers, then proceed to ethical analysis employing the four principles of biomedical ethics as a conceptual framework (Beauchamp and Childress, 2001). We conclude with a call for scientific advancement to proceed in tandem with ethical consideration, informed by empirical study of the views of high risk individuals and their families. This collaborative approach will help ensure that predictive testing progresses in an ethically acceptable manner that minimizes potential adverse effects and maximizes meaningful benefits for those at high risk of psychosis.

2. Current prediction methods

2.1. Clinical and familial high risk groups

The last three decades have witnessed considerable progress in the

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application of biomarkers, demographic risk factors, and symptom profiles to predict the development of psychosis. Current research models focus on risk prediction within high risk groups, a narrowing of inclusion criteria necessitated by the relatively low incidence of psychosis within the general population (Yung and Nelson, 2013). High risk individuals are categorized into 'clinical high risk' (also known as 'ultra high risk'), and 'familial high risk'. Clinical high risk groups comprise of those with low grade 'pre-psychotic' symptoms, variously described as 'attenuated psychotic symptoms' or the 'at risk mental state'. These symptoms do not meet diagnostic criteria for schizophrenia or other psychotic disorders, either due to their non-specific nature or short-lived course (Fusar-Poli et al., 2013). Subthreshold symptoms have been repeatedly shown to be independently predictive of transition to psychosis at rates of up to 39% over a two-year period (Fusar-Poli et al., 2016). Admittedly, heterogeneity exists between studies in the definition of transition to psychosis, largely due to variation in diagnostic criteria, thus limiting the generalizability of results (McGorry et al., 2018). However, ongoing large consortia-based projects (most notably PRONIA and PSYSCAN, which include multiple global sites) aim to redress this issue (S Tognin et al., 2019; Koutsouleris et al., 2018). Familial high risk groups consist of individuals at presumed elevated genetic risk, traditionally determined through degree of relatedness to an affected individual (Johnstone et al., 2002; Erlenmeyer-Kimling et al., 1997; Jørgensen et al., 1987). Notably, there is a degree of crossover between clinical and familial high risk groups (Smieskova et al., 2013). Fundamentally, it is possible to reliably identify a group of, generally, young individuals who present with overlapping clinical and/or genetic risk markers and are thus at elevated risk of developing psychosis (Johnstone et al., 2002; Fusar-Poli et al., 2012). Recent advances employ machine learning in conjunction with neuroimaging and genetic biomarkers, and clinical risk factors to quantify psychosis susceptibility with increased accuracy.

2.2. Neuroimaging biomarkers

A number of key neuroimaging biomarkers have been consistently found to predict transition to psychosis. In keeping with the theory of psychosis (schizophrenia in particular) as a disorder of the developing brain, characteristic changes appear dynamic over time (Takahashi et al., 2009; Cannon et al., 2015; Sun et al., 2009). In fact, it is the evolving nature of many gray matter abnormalities that is most predictive of transition to psychosis, rather than any abnormality in isolation (Bois et al., 2015).

Reduced gray matter density within cortical regions including the temporal lobes, frontal lobes, cingulate gyri, and hippocampi has repeatedly demonstrated predictive properties for psychosis (Fusar-Poli et al., 2012). In addition, meta-analysis of studies utilizing voxel-based morphometry revealed reduced gray matter volume in the insula, cerebellum, anterior cingulate cortex, and the prefrontal cortex as being predictive of onward transition to psychosis (Smieskova et al., 2010).

Furthermore, there is a growing body of evidence indicating the presence of neurophysiological functional changes in individuals at high risk of psychosis (Lin et al., 2019). A small number of studies utilizing fMRI in high risk individuals have found significant differences in brain regional activation during neurocognitive task performance, and variation in functional connectivity in the resting state at baseline in those who subsequently transition to psychosis compared with those who do not (Whalley et al., 2006; Sabb et al., 2010; Anticevic et al., 2015). In addition, a small number of PET studies of high risk cohorts demonstrate increased presynaptic dopamine synthesis capacity in the striatum and brain stem in the group who subsequently transition to psychosis versus those who do not (Howes et al., 2011; Allen et al., 2012). Further longitudinal functional imaging studies are undoubtedly indicated, nevertheless recent work suggests that this approach may add predictive power to risk models (Hunter and Lawrie, 2018).

Overall, significant advances have been made in elucidating the neuroimaging findings indicative of future transition to psychosis. The predictive accuracy achievable reflects this progress: a balanced accuracy of 88% in differentiating between high risk individuals who transition compared to those who do not has been demonstrated using sMRI alone, and up to 94% when combined with clinical markers (Zarogianni et al., 2017). However, thus far studies have been small, and variability exists between groups. Therefore, a definitive collection of neuroimaging biomarkers that reliably indicate risk of transition to psychosis remains to be established (Smieskova et al., 2010; Lawrie et al., 2011). Future work is likely to focus on optimizing the accuracy of predictive models by combining neuroimaging biomarkers with other modalities (S Tognin et al., 2019).

2.3. Genetic biomarkers

The central role of genetics in the etiology of schizophrenia and psychosis is well established (Gottesman, 1991; Hilker et al., 2018). Recent years have witnessed a paradigm shift in psychiatric genetics research towards large consortia led genome wide association studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium., 2014; Purcell et al., 2009). These have advanced understanding of the polygenic nature of psychiatric disorders, facilitating the development of polygenic risk scores (PGRS) (Neilson et al., 2018). PGRS can be applied independently or in conjunction with other biomarkers to more accurately quantity genetic risk beyond the level of simple relatedness. One recent study demonstrated elevated polygenic risk scores for schizophrenia (PGRS-SCZ) in individuals in a familial high risk cohort who transitioned to schizophrenia, compared to those who did not (Neilson et al., 2018). Moreover, increased PGRS-SCZ was found to be significantly associated with increased gyrification within the frontal lobes bilaterally (Neilson et al., 2018). These promising early results in this rapidly developing field illustrate the interconnectedness of genetic and neuroimaging biomarkers, and suggest that, in future, they could in combination serve as a clinically useful predictive tool.

2.4. Multivariate models

Multivariate models of psychosis risk integrate multiple demographic, clinical, neuroimaging, and genomic findings into potent and accurate risk prediction tools. Recent multivariate models have shown accuracy in high risk groups comparable to that of established cardiac, oncological, and orthopedic risk calculators (Cannon et al., 2016; Carter et al., 2002; Shah et al., 2012; Cannon et al., 2008).

3. Ethical analysis

Ethical evaluation in the field of predicting psychosis thus far has predominantly focused on the issues raised by the identification of clinical high risk groups using symptom scales within a research context (Corcoran et al., 2005; Mittal et al., 2015; Heinssen et al., 2001; Morris and Heinssen, 2014; Corcoran, 2016; Lysaght et al., 2012). This paper furthers existing discussion through in-depth consideration of the implications of the clinical application of predictive tools, and evaluation of the ramifications of newer multivariate predictive models incorporating neuroimaging. The four principles of biomedical ethics are employed as a conceptual framework for analysis, namely: respect for autonomy, non-maleficence, beneficence, and justice (Beauchamp and Childress, 2001).

4. Respect for autonomy

The principle of respect for autonomy requires the clinician to proactively support individuals in making and acting upon independent decisions regarding psychosis prediction (Beauchamp and

Childress, 2001). Autonomy based considerations are particularly salient at the time of consent for testing and disclosure of results (including both intended and incidental findings).

4.1. Informed consent

Informed consent upholds autonomy by safeguarding against medical paternalism. Three components are essential for valid informed consent: adequate information; capacity to consent; and voluntariness. We consider how each component can be fulfilled in the context of psychosis risk prediction.

4.1.1. Adequate information

In the UK, the standard of information disclosure required for consent has recently changed from that which a responsible body of clinicians would support disclosing to what a 'reasonable person in the patient's position would be likely to attach significance to' (Bolam v Friern Hospital Management Committee; Montgomery v Lanarkshire Health Board; Chan et al., 2017). When deciding whether to undergo predictive testing for psychosis the 'reasonable person' standard is likely to include, at a minimum, the nature of the condition predicted, the accuracy of the predictive tool, and the likely costs and benefits of knowing one's degree of risk (Heinssen et al., 2001; Morris and Heinssen, 2014). Each of these topics warrants further consideration.

Firstly, the condition predicted is not well defined, as many studies include a range of different diagnoses with varied treatments and prognoses under the outcome of psychosis (Hunter and Lawrie, 2018; Lawrie et al., 2019). Therefore, until such a time when predictive tools can distinguish between different types of psychotic illness with accuracy, the heterogeneity of diagnoses encompassed by this term must be clearly conveyed, and effort made to avoid the misperception that psychosis is synonymous with schizophrenia (Heinssen et al., 2001; Heinimaa and Larsen, 2002; Biesecker and Peay, 2003). In addition, individuals at high risk for psychosis also have significantly increased susceptibility to non-psychotic disorders, adding greater complexity to the meaning of a high risk prediction, which further demands skilled communication to convey (Lawrie et al., 2019).

Moreover, the 'reasonable person' standard demands that information be tailored to the individual in question (Chan et al., 2017). Thus, it is important to take into account variability in pre-existing knowledge of psychosis. Some individuals may have misperceptions borne of societal stigma which need debunked through education, whereas others are likely to be well-informed by virtue of having affected relatives. Nevertheless, the variability of the same diagnosis between individuals needs to be communicated (Biesecker and Peay, 2003).

Furthermore, it should be made explicit that predictions are inevitably uncertain (Biesecker and Peay, 2003). Clinicians should be cognizant of the fact that abstract risk predictions can be misinterpreted, and time and effort should be afforded to ensuring that the probabilistic nature of predictions is well understood, to counteract the tendency to conceptualize risk as a falsely dichotomized prediction that psychosis will or will not develop (Lysaght et al., 2012; Biesecker and Peay, 2003).

Lastly, a realistic understanding of the possible benefits and disadvantages of learning one's risk status must also be conveyed, with explicit recognition of where evidence is lacking to ensure the potential therapeutic gain is not oversold (Heinssen et al., 2001; Heinimaa and Larsen, 2002). Personal reflection on the psychosocial impact of obtaining such knowledge should also be encouraged (Corcoran et al., 2005; Biesecker and Peay, 2003).

4.1.2. Capacity

Decision-making capacity for predictive testing requires careful consideration for a number of reasons. Firstly, those at high risk for psychosis can have significant levels of comorbid psychiatric disorders, intellectual disabilities, and subthreshold psychotic symptoms, all of which are potentially (though not inevitably) capacity impairing (Mittal et al., 2015; Heinssen et al., 2001; Corcoran, 2016; Lawrie et al., 2019; McGorry et al., 2001). Of note, provision of extra time and explanation has been shown to facilitate capacity in those with established schizophrenia, leveling off the disparity with unaffected controls (Heinssen et al., 2001; Morris and Heinssen, 2014; McGorry et al., 2001). Therefore, generalized conclusions regarding decision-making capacity in individuals with mental disorders cannot be drawn, instead case-by-case assessment in a maximally supportive environment is indicated.

Given the typical age of onset of psychosis, predictive testing is likely to predominantly target adolescents, raising further questions surrounding capacity. In the UK, decision-making capacity in minors is addressed by the concept of Gillick competence, whereby children aged under 16 years can have capacity to consent, provided they demonstrate sufficient maturity and intelligence to understand and appraise the proposed intervention (Gillick v West Norfolk & Wisbech AHA & DHSS; Wheeler, 2006). For minors deemed not to be Gillick competent (and adults who lack capacity due to mental illness) questions arise regarding whether parents or advocates should have the power to give proxy consent for psychosis prediction, as is generally the case for interventions which are deemed to be in the minor's best interests (General Medical Council 2018).

In the field of clinical genetics, predictive testing of minors for adult-onset conditions is contra-indicated, unless interventions in childhood can prevent or ameliorate illness (Biesecker and Peay, 2003; Lucassen and Hall, 2019). The ethical reasoning behind this is that allowing a child to make their own decision regarding testing when they reach adulthood respects their future autonomy and protects their right to an open future (Feinberg, 1980). In the case of psychosis prediction it is uncertain whether the therapeutic gain from pre-emptive interventions in childhood or adolescence is compelling enough to justify restricting future autonomy in this manner. Moreover, given the typical adolescent or early adult onset of psychosis it does not obviously fit the paradigm of either an adult or childhood-onset condition.

4.1.3. Voluntariness

The final essential component of informed consent is voluntariness. Individuals at high risk for psychosis may be vulnerable to coercion due to subthreshold psychotic symptoms, comorbid psychiatric disorders, or intellectual disability. Persuasion from well-meaning relatives may be difficult to distinguish from coercion, particularly given this vulnerability. Moreover, due to the heritability of psychosis, revealing the risk status of one individual potentially implicates family members, who may therefore have personal interests in encouraging or dissuading testing. In addition, clinicians may harbor unconscious bias in favor of pursuing risk prediction out of zeal for clinical innovation, and desire to further understanding of psychosis etiology (Corcoran et al., 2005). However, screening programs for conditions such as Huntington's Disease and breast cancer susceptibility illustrate that many people would rather not know their level of risk (Corcoran et al., 2005; Lawrie et al., 2012). Thus, individuals must be equally well supported in declining to undergo predictive testing.

4.2. Disclosure of results

4.2.1. Risk predictions

Respecting autonomy also necessitates disclosing risk predictions in a manner which is sufficiently explicit to support meaningful decision-making based on the results, while avoiding engendering hopelessness. Existing services for those at clinical high risk advocate a 'hopeful and competent' stance in risk disclosure and discussion, whereby the onus is placed on the treatability and normalization of psychotic disorders (McGorry et al., 2001). In reality, there is minimal empirical research examining how individuals react to personal risk predictions and little to guide how best to disclose predictive information in a manner that

maximizes autonomy (Biesecker and Peay, 2003).

4.2.2. Incidental findings

In addition to risk prediction results, tools employing neuroimaging and/or genetic investigations may also give rise to clinically relevant incidental findings. A recent review demonstrated the presence of incidental findings in 22% of sMRI brain scans obtained in a research context (O'Sullivan et al., 2018). Fortunately, the majority of incidental findings on neuroimaging are benign, with further studies indicating that only 3 to 8% of research MRI scans required onward referral for further assessment or management of incidental findings (Katzman et al., 1999; Kim et al., 2002). Of particular note, the rates of incidental cerebral malignancies are extremely low (O'Sullivan et al., 2018).

Nevertheless, incidental findings in the context of psychosis prediction have significant implications for informed consent, and results disclosure. Firstly, in order to facilitate shared decision-making, the likelihood of incidental findings and their probable clinical significance should be discussed in advance of the decision to consent for risk prediction (O'Sullivan et al., 2018). Moreover, a patient's right to decline to be informed about particular clinical findings is a widely accepted tenet of medical ethics and law, in line with the principle of respect for autonomy (Heinrichs, 2011). However, it is contentious as to whether this right should extend to the rare instances in which the incidental finding is life-threatening or comparably risky, as non-disclosure may consequently infringe on the clinician's duty to avoid causing harm (Heinrichs, 2011).

5. Non-maleficence

The principle of non-maleficence requires the clinician to avoid causing harm that is disproportionate to the benefits of psychosis risk prediction (Beauchamp and Childress, 2001). Multiple harms must be minimized, including: neuroimaging associated risks; stigma; overmedicalization; misleading results; and threats to data privacy.

5.1. Neuroimaging risks

The neuroimaging modalities employed in current psychosis risk prediction models are generally well-tolerated. Nevertheless, a number of associated risks warrant further consideration. Physical risks of MRI include the displacement or malfunction of implanted medical devices due to potent magnetic forces; radiofrequency related skin burns; and noise exposure (European Society of Radiology (ESR) 2019). These risks can be minimized through detailed patient screening and vigilant adherence to safety precautions (Greenberg and Hoff, 2019). PET scanning has a differing risk profile associated with exposure to radiation, albeit at low levels, due to the short half-life of radioisotopes administered (Downie and Marshall, 2007).

Furthermore, concerns have been voiced regarding the potential for psychological harms associated with undergoing neuroimaging, especially MRI. In children and adolescents in particular, scanning has been linked with anxiety, fear, and distress due to claustrophobia (Downie and Marshall, 2007; Jaite et al., 2019; Schmidt et al., 2011). However, such fears have not been substantiated by recent empirical research, which established similarly low levels of anxiety experienced during brain MRI by children and adolescents, compared to adult populations (Jaite et al., 2019).

5.2. Stigma

Sadly, mental illness continues to attract societal stigma, and identifying individuals as high risk for psychosis may incur similar negative attitudes (Corcoran et al., 2005; Corcoran, 2016; Sisti and Calkins, 2016). Stigma exists in a number of forms, including self-stigma, whereby the individual internalizes negative views, prompting self-imposed limitations on aspirations (Heinimaa and Larsen, 2002). Well-meaning family members might discourage the pursuit of longer term plans such as higher education, and attempt to minimize stress by prohibiting risk-taking behaviors inherent to personal growth in adolescence (Heinssen et al., 2001; Lawrie et al., 2019; Sisti and Calkins, 2016). In addition, external discrimination in the form of restricted employment opportunities and curtailed relationships may occur (Corcoran et al., 2005; Biesecker and Peay, 2003). Moreover, the stress associated with experiencing stigma may increase risk of progression to psychosis or schizophrenia (Mittal et al., 2015; Lawrie et al., 2019). A qualitative study of the attitudes of young people at clinical high risk for schizophrenia towards predictive genetic testing echoed concerns that a high risk result could cause them to internalize the 'sick role'; face workplace discrimination; and damage relationships (Lawrence et al., 2016).

However, minimizing stigma requires nuanced consideration, as evidence suggests that in high risk individuals the overt display of symptoms of mental illness, as opposed to the high risk label in itself, generates greater shame and discrimination (Corcoran, 2016). Therefore, if risk prediction can expedite detection and treatment of psychotic symptoms, it could lessen the overall stigma experienced by the individual (Corcoran et al., 2005; Mittal et al., 2015; Heinimaa and Larsen, 2002; McGorry et al., 2001).

5.3. Over-medicalization

Psychosis risk prediction raises challenging questions regarding what level of susceptibility constitutes high risk and justifies intervention (Heinimaa and Larsen, 2002; Lawrie et al., 2012). Psychosis risk exists on a spectrum, with no clear boundary demarcating normal from pathological – thus, labeling people as 'high risk' could leave clinicians open to accusations of over-medicalization, whereby a non-medical problem is redefined and treated as a disorder (McGorry et al., 2001; Conrad, 1992).

5.4. Misleading results

Existing ethical discussion is permeated by concern regarding false-positive results, stemming from findings that approximately two thirds of those deemed high risk using symptom-based prediction tools do not transition to psychosis during follow up (Fusar-Poli et al., 2012; Nelson et al., 2013). These individuals are vulnerable to stigma, overmedicalization, and intervention side-effects, without possibility of therapeutic gain. False-negative results could also incur harm through disincentivizing behavioral change such as avoidance of illicit drug use; and delaying access to services in the event of symptom onset (Lawrie et al., 2019; Robinson et al., 2011).

As clinically useful biomarkers emerge focus is shifting towards individualized risk calculations for psychosis, whereby results are presented as a probabilistic prediction, rather than a binary assessment of high risk or not (Lawrie et al., 2019). The issue then evolves from one of false positives and negatives, to that of predictive power (Heinimaa and Larsen, 2002). Multivariate models endeavor to deliver a higher predictive power than tools based on clinical data alone (S Tognin et al., 2019). Nevertheless, predictions remain approximate, and it is yet to be established at what threshold of predictive accuracy results are considered meaningful and useful to individuals.

5.5. Data privacy

The drive towards multivariate prediction models relies on big data aggregated across centers (Lawrie et al., 2012). Data-sharing raises questions of how to ensure informed consent for the myriad future uses of personal data. The concept of broad consent (whereby individuals are prospectively made aware of the type of data stored; time period for this; and types of future sharing and use) attempts to balance autonomy

with recognition of the scientific benefits of allowing future, secondary use of existing data (Fisher and Layman, 2018).

In addition, skull and cortical imaging, and whole genome sequences are potentially identifiable. The threat to anonymity is heightened when such data is linked, as could be the case in multivariate prediction models (Lawrie et al., 2019; Fisher and Layman, 2018). The small body of empirical research available suggests that those at high risk for psychosis feel apprehensive about information security and privacy of genetic risk information (Lawrence et al., 2016).

6. Beneficence

In accordance with the principle of beneficence, the benefits of predictive testing for psychosis should outweigh the risks and costs (Beauchamp and Childress, 2001). Therefore, ethical analysis requires evaluation of the prospective gains, including: self-empowerment; early intervention; potential prevention of transition to psychosis; and enhanced prognostication.

6.1. Self-empowerment

Knowledge of one's psychosis risk status can be considered empowering, as it enables self-education about psychosis; motivates avoidance of modifiable risk factors (such as illicit drug use and stress); facilitates peer support; and heightens self-understanding of subthreshold psychotic symptoms (Mittal et al., 2015; Lawrie et al., 2019; Lawrence et al., 2016). Fore-knowledge also creates a window of opportunity to make future wishes known, potentially through an advance statement, to maximize autonomy in the event of subsequent loss of capacity through illness (Mittal et al., 2015). Those found to have low susceptibility could benefit from reassurance in the face of non-psychotic symptoms or a positive family history (Lawrie et al., 2019).

6.2. Early intervention

Moreover, high risk individuals who are predicted to transition to psychosis could benefit from targeted follow-up to rapidly detect the onset of psychotic symptoms. The optimal method of delivering such follow-up is yet to be established, with options ranging from educating the patient and relatives on early symptoms of psychosis and encouraging self-reporting, to the more invasive alternative of regular contact with an early intervention service (EIS) to monitor mental state. Minimizing the duration of untreated psychosis (DUP) is associated with an improvement in clinical and functional outcomes compared to those who experience treatment delay (Lieberman et al., 2019; Hegelstad et al., 2012). Nevertheless, a balance should be sought between facilitating prompt intervention, while avoiding overshadowing what may be an individual's last pre-symptomatic years with stigma, anxiety, and medicalization.

Additional benefits of engagement with EIS prior to the onset of overt psychosis include decreased overall rates of hospital admission, and a lesser frequency of compulsory admission, compared to patients with established first episode psychosis (FEP) at initial presentation (Valmaggia et al., 2015). Furthermore, ongoing management in an EIS setting has been demonstrated to result in lesser treatment discontinuation, lesser disruption to education and employment, and lower symptom severity at the end of the treatment course, compared with treatment out with a specialized service (Correll et al., 2018). In addition, the collaborative, individualized approach adopted by EIS teams is valued by patients and families (Lester et al., 2011; Lavis et al., 2015). Nevertheless, these prospective benefits are presented with the caveat that the evidence base for many interventions typically delivered as part of the EIS model, such as phase-specific cognitive behavioral therapy (CBT) and family therapy in FEP is lacking, and subsequent trials are indicated (Marshall and Rathbone, 2011). Moreover, a number of studies indicate that the improved clinical and functional outcomes associated with EIS are not sustained in the longer term, particularly following discharge back to generic psychiatric care (Chang et al., 2017; Gafoor et al., 2010; Bertelsen et al., 2008).

6.3. Preventing transition

The ultimate ambition of prevention research is to avert (or delay) the development of psychosis. Currently, no specific intervention has a robust evidence base as a primary prevention agent for those at high risk (Lieberman et al., 2019; Stafford et al., 2013; Kuharic et al., 2019). Nevertheless, CBT has been demonstrated to reduce transition to psychosis (both alone and in conjunction with family intervention), however the evidence in support of this is admittedly of variable quality (Stafford et al., 2013; Kuharic et al., 2019). Similarly, integrated psychotherapy shows an association with preventing transition, with the caveat of a low quality evidence base (Stafford et al., 2013). Lastly, one small study suggests that omega-3 fatty acids may prevent psychosis, however this effect has not been well-replicated (Stafford et al., 2013; Kuharic et al., 2019). Contrastingly, antipsychotic medications have shown little efficacy in primary prevention (Stafford et al., 2013; Kuharic et al., 2019). Overall, while a number of interventions show early promise, more methodologically robust, larger studies are indicated to provide a reliable evidence base regarding the efficacy of primary prevention for those at high risk of psychosis.

In addition to efficacy, interventions must prove acceptable to individuals in terms of side-effect profile (Heinimaa and Larsen, 2002). This is particularly problematic in the case of antipsychotics, with short-term considerations such as extrapyramidal side effects, hyperprolactinemia, sedation, and weight gain, and longer term potential consequences of tardive dyskinesia, diabetes and cardiovascular disease (Corcoran et al., 2005; Heinssen et al., 2001; Sisti and Calkins, 2016). Moreover, the lack of clinical trials of antipsychotic use in the sensitive developmental period of adolescence adds an element of uncertainty to the potential long-term effects (Heinimaa and Larsen, 2002). Alternatives to antipsychotics, such as CBT and omega-3 fatty acids have more palatable risk profiles (Corcoran et al., 2005; Mittal et al., 2015).

6.4. Prognostication and targeted intervention

In recent years, research on those at high risk of psychosis has broadened in scope beyond predicting transition, to investigate neuroimaging biomarkers associated with other salient outcomes in this cohort, such as social and occupational functioning (Koutsouleris et al., 2018). Functional outcomes are deemed particularly significant in this cohort, as the high risk state can be associated with neurocognitive and functional deficits. These can have marked personal and socioeconomic implications, even among individuals who do not transition to psychosis. One study utilizing baseline sMRI in a high risk group evidenced lower gray matter density in bilateral frontal and limbic areas, and left cerebellar declive, in association with poorer functional outcomes at medium to long-term follow-up, independent of transition to psychosis (Reniers et al., 2016). Furthermore, machine learning models combining baseline neuroimaging and clinical findings have demonstrated the ability to predict impaired social functioning at 1-year follow-up correctly in up to 83% of individuals in a high risk cohort, thus outperforming human prognostication (Koutsouleris et al., 2018). The ability to reliably predict which high risk individuals are likely to experience functional impairment could facilitate targeted psychosocial support at an early stage, with the aim of averting poor outcomes (Reniers et al., 2016).

7. Justice

Justice demands that the benefits, costs and risks of predictive testing for psychosis are distributed fairly among individuals, such that no-one is unduly advantaged or disadvantaged by this intervention

(Beauchamp and Childress, 2001). Ensuring parity in the context of a publicly funded health service with finite resources requires predictive testing be cost-effective; equally accessible to all; and delivered in a manner that avoids reinforcing structural biases.

7.1. Cost-effectiveness

Cost is a core consideration when implementing screening programs. Predicting transition to psychosis holds the potential to deliver cost savings by enabling early intervention and its associated improved outcomes. EIS has been shown to be cheaper than non-specialist community mental health teams when assessing direct cost to the NHS, largely via reduced length of mental health inpatient admissions (Tsiachristas et al., 2016). When the wider societal cost of illness is considered greater savings could be achieved. A systematic review identified evidence in support of the cost effectiveness of EIS, however the authors commented that the evidence base remains relatively small and heterogenous, thus identifying a need for further well-constructed studies (Aceituno et al., 2019).

Furthermore, the expense of investigations involved in psychosis risk calculation, such as neuroimaging, must also be factored into cost-effectiveness analyses. Recent research indicates that the use of standard sMRI with the indication of ruling out treatable organic causes in patients presenting with FEP is not financially viable, despite this modality being relatively widely available (Tsiachristas et al., 2016; Valmaggia et al., 2009). However, this finding cannot necessarily be generalized to the case of psychosis risk prediction. Other potentially useful neuroimaging modalities in prediction, such as PET, remain comparatively inaccessible and prohibitively expensive (Abi-Dargham and Horga, 2016). Overall, there is a paucity of data regarding the cost-effectiveness of neuroimaging and other resources, necessary for the clinical implementation of psychosis susceptibility screening.

7.2. Equity of access

Currently, the neuroimaging and genomics capabilities required for multivariate models of psychosis risk are largely isolated to research centers in developed countries (Lawrie et al., 2019; Corsico, 2019). In the meantime, the design of adapted versions of predictive tools excluding less widespread modalities could help widen access to screening (Lawrie et al., 2012).

The task of accessing high risk individuals to offer predictive testing poses a further challenge to distributive justice. The majority of those who develop schizophrenia are not obviously at high familial or cognitive risk (Lawrie et al., 2012). Moreover, given the prevalence of subthreshold psychotic symptoms in this group, high risk individuals may be particularly difficult to engage due to social withdrawal, decline in functioning, and poor insight (McEvoy et al., 2006; Gronholm et al., 2017). The stigma associated with mental health services poses another significant barrier to service engagement, leading to widespread efforts to ensure that prodromal psychosis services are discretely named and located in neutral, community spaces (Corcoran et al., 2005; Heinssen et al., 2001; McGorry et al., 2001; Norman et al., 2004).

Existing prodromal psychosis services proactively encourage referral of potentially high risk individuals through links with primary care; emergency services; and non-clinical community services (e.g. schools and criminal justice agencies) (Ajnakina et al., 2017). Despite this, a recent study of one UK trust found that only 4.1% of those with FEP had previously engaged with prodromal services (Ajnakina et al., 2017). Therefore, even if accurate prediction and effective preventative interventions were a clinical reality, targeting the population currently served by prodromal services would avert few instances of transition to psychosis. Moreover, concerns were raised regarding inequality in access to prodromal services as 77% of referrals were received from GPs and healthcare workers, potentially disadvantaging those who are less likely to be registered with a GP, such as migrants (Ajnakina et al., 2017). Previous studies have found further disparities in access to services, including an association between greater geographical distance from service location and longer DUP (Kvig et al., 2017).

7.3. Algorithmic bias

Machine learning has the potential, if reliably calibrated, to reduce the impact of clinical bias in healthcare (Martinez-Martin et al., 2018). However, machine learning algorithms could equally reinforce existing structural biases depending upon how they account for factors such as socioeconomic status and race (Corsico, 2019; Martinez-Martin et al., 2018). The influence of such biases in existing psychiatric diagnostic practice has been widely discussed (Schwartz and Blankenship, 2014). Heightened concerns arise due to the perceived lack of transparency in machine learning, whereby it is possible for neither the clinician nor the patient to be aware of the how the prediction is generated, thus precluding questioning of it. This could curtail shared decision-making and impede trust. Clinicians employing machine learning in psychosis prediction should be well-informed regarding how the algorithm is developed; the data on which it is based; and its limitations, in order to critically appraise its outcomes (Martinez-Martin et al., 2018).

8. Conclusion

The rapidly developing field of psychosis prediction holds promise of meaningfully improving clinical outcomes for those at high risk of psychosis. Structural and functional neuroimaging has a central role in optimizing the predictive power of current risk models. However, it is imperative that such scientific innovation proceeds in tandem with ethical consideration. This paper furthers existing ethical discussion by considering the ramifications of the clinical application of predictive tools, and evaluating the ethical implications of newer risk models incorporating neuroimaging. Ethical priorities include, firstly, ensuring predictive testing is carried out in a manner which promotes autonomy through valid informed consent, and meaningful disclosure of results. Secondly, minimizing the risks of neuroimaging, stigma, over-medicalization, misleading results, and compromised data privacy. Thirdly, promoting the prospective benefits of early intervention; avoidance of modifiable risk factors; heightened understanding of subthreshold psychotic experiences; access to education and peer support; opportunity for advanced planning; and enhanced prognostication. Finally, upholding distributive justice by ensuring cost-effectiveness; facilitating equal access to testing; and avoiding reinforcement of structural biases. Empirical study of the views of those who have most at stake in predictive testing, namely high risk individuals and their families, is crucial to achieving these aims. Ultimately, continued scientific progress alongside empirically informed ethical analysis will allow us to preempt adverse effects and maximize the great potential benefits of predictive testing for individuals at high risk of psychosis.

Author contributions

NL conducted the ethical research and analysis, planned and co-prepared the initial draft of the manuscript, and was primarily responsible for the subsequent re-drafting and revision of the final manuscript. SH researched and reviewed the scientific background and practical issues, and planned and co-prepared the initial draft of the manuscript. SL developed the concept of the paper, provided supervision, and reviewed and edited the final manuscript.

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Declaration of Competing Interests

The authors have no relevant conflicts of interest to declare.

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