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Prodromes and Preclinical Detection of Brain Diseases: Surveying the Ethical Landscape of Predicting Brain Health

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Abstract (Word count 205)

The future of medicine lies in disease modification and prevention. The science of preclinical detection is young, but moving rapidly. Preclinical interventions offer the hope to decrease the severity of a disease or delay the development of a disorder substantially. With such promise, the research and practice of detecting brain disorders at a preclinical stage present unique ethical challenges, challenges that must be addressed to ensure the benefit of these technologies. Direct brain interventions have potential to impact not just what a patient has but who they are and who they could become. Further receiving an assessment for a preclinical or prodromal state has potential to impact perceptions about capacity, autonomy and personhood and could become entangled with stigma and discrimination. Discussion of the risks and benefits of the emerging technology will focus on how to ensure beneficence by presenting the limitations of preclinical detection and by contextualizing the risk associated with preclinical status. Exploring ethical issues alongside and integrated into the experimental design and research of these technologies is critical. This review will highlight ethical issues attendant to the current and near future states of preclinical detection across the life span, specifically as it relates to autism spectrum disorder (ASD), schizophrenia, and Alzheimer's disease.

Significance Statement:

Preclinical interventions in developing brain disorders offer the strongest promise of delaying, modifying, or preventing the development of clinical disorders. Although promising, intervening at early stages in disorders inherently linked to identity and personhood presents unique ethical challenges. These challenges must be addressed before the practices are implemented. Both the treatment and the diagnosis itself have the potential to profoundly impact patients. We contextualize the risk of diagnosing preclinical states and present the limitations of preclinical interventions to guide research and policy as the field of preclinical detection rapidly expands.

1. Introduction

Early intervention and disease modification are the future of healthcare worldwide. The ethical issues, rather than the technical and regulatory issues, associated with detecting these prodromal or preclinical states may pose the greatest threats to this effort. Detecting diseases and disorders before clinical symptoms manifest enables earlier intervention and offers the hope of improved health outcomes. Breast cancer is an example in which screening for markers before symptoms arise is both widespread recommended by many physician groups (Monticciolo et al., 2017; Sardanelli et al., 2017). Earlier interventions reduce average patient cost by more than $100,000 over two years (Blumen et al., 2016) and decrease mortality (Howlader et al., 2017). Such a large positive effect of early detection and treatment seems to provide an almost incontrovertible argument for regular early screenings. Even so, the method of arriving at an early intervention is controversial. There is conflicting evidence on the efficacy of routine mammograms in decreasing breast cancer mortality (Berry et al., 2005; Domchek et al., 2010; Narod et al., 2014; Harding et al., 2015; Monticciolo et al., 2017). The ongoing debate over the necessity of regular screenings for breast cancer in average-risk women demonstrates the complexities that arise from early detection efforts, even when treatments are widely available and effective. The debate becomes more complicated when effective treatments are not yet developed, as with brain disorders.

With the considerable global burden of brain disease, the promise of early detection and early intervention cannot be overstated. That being said, preclinical detection of brain disorders encompasses a unique suite of ethical concerns, as the dysfunction in the brain directly impacts behavior, and is intrinsically linked to identity and autonomy. In other words, when we are predicting a brain disorder, we are not only predicting one aspect of health, we are predicting who a person may become.

This review will discuss the considerations surrounding the ethics of preclinical detection through the lens of three brain disorders that typically present at distinct developmental time points across the life span: autism spectrum disorder (ASD) in early childhood, schizophrenia in adolescence, and Alzheimer's disease with aging populations. The patient, and his/her status in the community, is similarly impacted regardless of whether the disorder's etiology is an acute biological or a multifactorial biopsychosocial one, so disorders from both categories will be discussed together. Related discussions of the ethics of preclinical detection have been started in other venues, such as Baum (2016) and Chneiweiss (2017) We will expand the discussion and place a greater emphasis on the implications for patients of a medicalized preclinical state. The disorders we focus on demonstrate the unique ethical quandaries in: 1) risk/benefit analysis, 2) the possibility of stigma and discrimination, 3) responsibility and communication of risk. The review will conclude with recommendations for addressing these ethical challenges which we mean not to hinder research, but to anticipate and mitigate roadblocks ahead. As medical screenings and diagnostic tools continue to expand in scope and accuracy, an ethical framework will be necessary even in research and clinical settings where preclinical detection of brain disorders is not the primary goal. The nature of preclinical detection is inherently probabilistic, so certainty can never be fully achieved with these strategies, but citizens worldwide stand to greatly benefit from the scientific advancements offered by preclinical detection if interventions and regulation are developed appropriately. We believe addressing these ethical concerns in anticipation and as part of the improvements to preclinical detection technology will help ensure the promise of improved health that predictive technologies aspire to offer.

2. Terminology: preclinical or prodromal brain disorders

Brain disorders are contextualized states, regardless of etiology. Disordered states that lead to disordered behavior are diverse in their development and manifestation, and some of these states are not universally seen as truly disordered (e.g. the prominent neurodiversity movement in the ASD community, see Armstrong (2015)). That said, all cases discussed here, and all cases in which preclinical detection could be used to identify patients before symptom onset, are medicalized, and are therefore subject to the same protection concerns and risks. The preclinical label is defined by the presence of predictive markers in the absence of symptoms that currently define the disease. Preclinical states are distinct from prodromal or sub-clinical states, in which some clinical symptoms (such as a mood disorder) are present but do not satisfy criteria for diagnosing a disorder (like schizophrenia) (Gourzis et al., 2002; Meyer et al., 2005) [see Table 1 for examples of preclinical and prodromal markers; adapted from Arias et al. (2018)]. Current early interventions target the prodromal stage in schizophrenia. In ASD, the hope is for early interventions to begin at the age when the child's behavioral symptoms do not reach diagnostic criteria. Efforts in Alzheimer's Disease are therefore unique, in that the preclinical stage is defined by an absence of behavioral or cognitive symptoms, well before the onset of Mild Cognitive Impairment (MCI). The definition and detection of preclinical stages are more accessible in disorders like Alzheimer's disease that have established molecular biomarkers (e.g. measuring amyloid levels with positron emission tomography and measuring tau levels in cerebral spinal fluid (Dubois et al., 2016); see Table 1) arising well before behavioral symptoms. Preclinical Alzheimer's disease is defined as the presence of one or more of these molecular biomarkers in the absence of cognitive impairment. The diagnosis is often sub-divided into two differential diagnoses: presymptomatic, for those who will develop clinical Alzheimer's disease with pathogenic autosomal mutations, and asymptomatic, for those at risk of developing clinical Alzheimer's disease with predictive biomarkers (Dubois et al., 2010). The reliability and validity of such tests will be further explored in the following section. In contrast to Alzheimer's disease, although many genetic and environmental factors have been identified for ASD and schizophrenia, no preclinical biomarkers for either disease have been validated to date. Current efforts for early detection in these diseases focus on identifying subclinical symptoms in the prodrome (Gourzis et al., 2002; Christensen et al., 2016)

3. The State of Preclinical Detection with Current Science and Assessment Techniques

Detection and assessment techniques for preclinical brain disorders are currently restricted to research efforts (including clinical trials); none are implemented in routine clinical practice. Even so, the use of "big data" medicine (e.g. whole-genome sequencing) expands the opportunity for preclinical detection to occur as a secondary outcome of an unrelated test or procedure. That said, the utility of early interventions is pushing clinicians to incorporate screening practices for early stages of disease.

Parents were historically the instigators of an eventual ASD diagnosis, but efforts to increase awareness and validate screening protocols have shifted the responsibility to clinicians. Although governmental recommendations do not support population screening procedures, many advising committees say otherwise (Committee on Children with Disabilities, 2001; Zwaigenbaum et al., 2015; 2017). A growing number of clinicians have adopted routine screenings as a part of their practice as a result (Palmer et al., 2011; Coury et al., 2017). Similarly, clinicians are now also recommended to screen older adults for early signs of dementia (McKhann et al., 2011; Cordell et al., 2013), and such screenings are covered by the American Medicare system. Recommendations for including biomarker screening for Alzheimer's disease is pending further validation of the methods. In contrast, there are no commonly implemented screenings for the development of schizophrenia before help-seeking is initiated by the patient or caregiver (Larson et al., 2010; Seidman et al., 2010).

Below, we will provide an overview of the state of preclinical and prodromal detection throughout the lifespan. Complementary, if somewhat separate, opportunities for early detection exists in the realm of digital phenotyping and incidental findings. Digital phenotyping relies on passive data collection from smartphone and other technology use to predict the development of brain and mental health disorders (Jain et al., 2015; Torous et al., 2016). Incidental findings refer to clinically relevant findings that were not the primary purpose of a diagnostic test. A significant body of scholarship has addressed how and whether to ethically disclose incidental findings, taking the perspectives of many stakeholders into account (Illes et al., 2004; Haga et al., 2012a, b; Wolf et al., 2012; Kleiderman et al., 2014). The ethical guidelines for incidental findings can serve as a model for how to incorporate preclinical detection, but new frameworks will be required. An incidental finding of a preclinical brain disorder has different social and personal implications than that of other diseases, and must be handled accordingly. Here, we will focus on the development and implementation of biomarkers for brain disorders. Although we focus on ASD, schizophrenia, and Alzheimer's disease given their prevalence and the significant amount of research ongoing in those fields, similar research exists for multiple sclerosis, Parkinson's Disease, Lewy Body Dementia, and other disorders. The rapid development of detection measures, pressure to implement them in clinical practice, and the ethical issues that are attendant even during the research phase warrant immediate discussion.

3.1 Autism Spectrum Disorder

ASD encompasses a range of phenotypes, from mild social impairment to an inability for self-sufficiency (2013). ASD is now estimated to affect 1 in 160 children globally (World Health Organization, 2017) and is the leading cause of disability in children under the age of 5 (Baxter et al., 2015). The average age of diagnosis is approximately 4 years old (Christensen et al., 2016), which makes the needs of patients and their caregiver(s) a great public health concern as well (Khanna et al., 2011; Cadman et al., 2012).

Studies have shown that infants who will develop autism have preferential looking at mouths versus eyes during social engagement (Jones and Klin, 2013). Early screening attempts for ASD rely on eye-tracking in infants to detect atypical patterns of social gaze. Retrospective analyses of eye tracking behavior have identified infants as young as 6 months of age who would later develop ASD (Chawarska et al., 2013; Jones and Klin, 2013; Shic et al., 2014). To date, these studies test the value of eye-tracking as a non-invasive and potentially relatively easy and inexpensive screening tool. These studies target high-risk populations (siblings of children with autism) of infants and children whose parents express concern over their child's social development (Sandin et al., 2014; Rowberry et al., 2015) Eventually, the hope is that such a tool could be implemented in routine wellness visits in all babies (high risk or not). Preliminary studies have also found differences in cortical development between infants who do and do not develop ASD (Hazlett et al., 2017). While brain scans may provide an opportunity for another preclinical biomarker of the disorder, neuroimaging is likely less accessible and too expensive to be considered for widespread screening. Early interventions to address early diagnoses are currently being designed. Perhaps unique to ASD treatment, the proposed behavioral interventions are beneficial for both autistic children and typically developing children (Institutes of Medicine and National Research Council, 2013), which minimizes the risk of false positives in this specific context.

3.2 Schizophrenia

Schizophrenia develops later in life, with the first symptoms usually appearing in late adolescence/early adulthood or during the peri-menopausal phase (Castle and Murray, 1993; World Health Organization, 2001). Positive symptoms (psychosis), negative symptoms (anhedonia), and cognitive deficits contribute to the severe disability and loss of productivity associated with the disorder (World Health Organization, 2001). Although the lifetime prevalence of schizophrenia is approximately 1% of the world population, the World Health Organization (WHO) estimates that schizophrenia is the 8th leading cause of Disability Adjusted Life Years (DALYs) in 15-44 year-olds (World Health Organization, 2001). Many risk factors of schizophrenia have been identified, including environmental (Cornblatt et al., 2003) and genetic (Ripke et al., 2014) contributors. Despite the genetic factors, genome-wide association studies (GWAS) show low sensitivity and specificity in identifying those who will develop schizophrenia, which has led some teams to warn against using genetic analyses as predictive tests (Ripke et al., 2014). No preclinical markers of schizophrenia have been identified; as such, clinicians rely on prodromal symptoms like anxiety, sleep disturbances, and depressive mood, to identify at-risk patients (Goulding et al., 2013).

At-risk patients are often identified because of treatment sought by the patient or caregiver, not by routine appointments. People often seek treatment for prodromal symptoms for schizophrenia, which are themselves clinical symptoms for other disorders (Gourzis et al., 2002;

Meyer et al., 2005; Rosen et al., 2006). At this stage, symptoms, family history, and genetic risk factors can combine to put the patient at high-risk for developing schizophrenia (Larson et al., 2010; Seidman et al., 2010; Goulding et al., 2013). This categorization presents the opportunity to intervene before clinical schizophrenia develops, in the interest of instigating preventative interventions. Prodromal symptoms do not always transition into clinical schizophrenia. Symptoms are often non-specific to psychosis (Gourzis et al., 2002; Rosen et al., 2006), and this has hindered success in designing early interventions. Prodromal interventions such as the use of atypical antipsychotics (McGorry et al., 2009), antidepressants (Cornblatt et al., 2007), and alternative treatments like omega-3 fatty acids (Amminger et al., 2010) have produced mixed success in reducing transition rates (Larson et al., 2010). The uncertainty of a prodromal diagnosis further limits the confidence of successfully intervening before clinical symptoms develop, especially given the severity of side-effects of anti-psychotic medications (Patel et al., 2014).

3.3 Alzheimer's disease

Alzheimer's disease is unique among the three disorders discussed here, in that there is a generally accepted symptomatic subclinical stage for this disorder (MCI), which is often preceded by the presence of amyloid-beta plaques, tau, and neurodegenerative biomarkers (Dubois et al., 2014; Jack et al., 2016; Racine et al., 2017). The research has progressed to the point that many organizations are advocating for the inclusion of a preclinical (fully asymptomatic) diagnosis being included in regular clinical practice (Dubois et al., 2014; Alzheimer's Association, 2019). Alzheimer's disease is the leading cause of dementia, and risk for this disorder increases dramatically with age (Hebert et al., 2013). Occurrence of the disorder is expected to double in the next 20 years, driven largely by the impending boom in population of those aged 65 or older (He et al., 2016). Ranked as the 25th most burdensome disorder in 1990, the increasing prevalence has driven Alzheimer's disease to become the 12th most burdensome disorder in the United States over the past 20 years (Alzheimer's Association, 2017). Similar increases in prevalence and burden are recorded throughout Europe (Wittchen et al., 2011). The protracted development of the disorder creates an enormous burden on the primary caregiver(s) and as many as 40% of whom suffer from depression (Alzheimer's Association, 2017).

In recent years, preclinical trials have commanded more of the industry's effort given the poor success rate of pharmaceutical trials in clinical interventions (Cummings et al., 2014; Hung and Fu, 2017). Dementia is thought to develop 20-30 years after the onset of amyloid-beta (Aβ) deposits in the brain (Hubbard et al., 1990; Jansen et al., 2015), strongly supporting the idea that effective treatments may require intervening at the preclinical stage. There are now multiple ongoing clinical trials that target high-risk populations for pharmaceutical interventions. For example, many drugs that previously failed efficacy trials in patients with mild to moderate Alzheimer's disease are now being retested in preclinical populations (Hung and Fu, 2017). High-risk populations are defined as individuals with a family history of Alzheimer's disease (Honea et al., 2012), the ε4 allele of the APOE gene (Bonham et al., 2016),or the presence of biomarkers like elevated tau and a high $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ ratio (Holland et al., 2012).

4. Balancing Risks and Benefits

4.1 Patient protection

Participants for trials of preclinical detection and/or treatment are most often recruited from "high-risk" populations, e.g. a family history of ASD or Alzheimer's disease, or a diagnosis of prodromal schizophrenia. Researchers and clinicians involved in these studies must therefore make conscious efforts to minimize the risk of coercion and to discourage unsubstantiated hopes that the research will personally benefit the participants, known as therapeutic misconception (Appelbaum et al., 1982). Research participants given a hypothetical high-risk status for Alzheimer's disease cited the desire to lower personal risk of developing dementia as a reason for enrolling in preclinical research more often than subjects given a normal risk status. The discrepancy between the groups remained even when informed that the efficacy of preclinical interventions has not been established (Grill et al., 2013). This evidence demonstrates that high risk populations are inherently vulnerable to have their judgment clouded by the promises of preclinical detection, and thus their autonomy and consent must be deliberately addressed. These protections against therapeutic misconception are the most commonly discussed, but the research community also stands to benefit from clarifying therapeutic misconceptions. "Research tourism," or the practice of enrolling in studies for the express purpose of obtaining diagnoses or treatments (Townsend and Cox, 2013; Gibson et al., 2017), certainly demonstrate the challenge of therapeutic misconception of many clinically-oriented scientific efforts. However, enrolling such patients could jeopardize the validity of the studies, since patients motivated by research tourism are likely to carry high-risk factors or be in the early stages of a disorder.

Any personal benefits that could be gained from preclinical detection are dependent on the current and future research in the science of therapeutic interventions. Reducing lifetime cost and minimizing suffering by intervening early are possible via preclinical detection. However, these outcomes are not guaranteed in ASD, schizophrenia, Alzheimer's disease or any other condition being explored for preclinical and prodromal markers. Evidence suggests that early interventions like Applied Behavioral Analysis (ABA) and antipsychotic treatment improve outcomes in ASD (Estes et al., 2015) and schizophrenia (McGorry et al., 2002; Woods et al., 2003; Kulhara et al., 2008), respectively. Even so, the positive effects of preclinical intervention are difficult to quantify. At best, successful interventions prevent the progression to clinical disease. Since all preclinical states are defined by a risk of progressing to the clinical disorder, large studies are required to statistically differentiate between patients who were successfully treated and those who would not have developed the disorder with or without treatment.

Given the early stages of this research, the limited personal benefits available to the patients must be emphasized in the consent process and by the research staff to ensure fully informed consent. Participating in research for personal health benefit is not unethical, but it is unethical for the research team to falsely inflate the benefits to incentivize participation. Even in the absence of overpromising, the public are active consumers of an optimistic and hyped media that offers its own priming for hope. This is why ongoing updates with multiple stakeholders and public scholarship must be integral to the research process.

4.2 Communication of information

Another challenge of communication happens during the research process wherein researchers face the dilemma of when and how much information should be communicated to the research participant. Decisions on whether to disclose preclinical status, considering its impact on identity and autonomy, must be considered with a deep knowledge of the specific population being served. Although some patients may appreciate the opportunity to plan for a developing disorder, others may find the diagnosis more distressing than helpful. When presented with the opportunity to participate in a hypothetical preclinical Alzheimer's disease study, participants were as likely to enroll whether or not they would be informed of their amyloid status (Grill et al., 2016). Still, the psychological effects of being given such information should not be assumed to be as inconsequential as the choice to receive it. Recognizing the potential for distress, the International Working Group (IWG) has recommended doctors not disclose preclinical Alzheimer's disease status by default, but only "when well-informed subjects request the information, in cases of high level of social responsibility and cognitive demand or in cases of inclusion in research protocols and clinical trials" (Dubois et al., 2016). Here is the primary difference between a disclosure of a pre-clinical diagnosis and an incidental finding in such research efforts like as brain imaging or whole-genome sequencing. In those cases, many argue that it is unethical to withhold incidental findings when the finding would trigger a specific course of action and treatment (Chneiweiss, 2017). That argument is not applicable to a preclinical state, because there are not any currently proven courses of action to treat a preclinical state. Therefore, the decision of whether to have a preclinical state disclosed to the patient must be a part of the consent process, and the choice should not dictate a patient's participation in the study or trial. Such recommendations only address the choice of participants knowing their status; more protections will be necessary once the screening technology expands beyond the research sector and into commercial opportunities.

Many clinicians hope that disclosing high risk or preclinical status will promote health-positive behaviors in patients hoping to mitigate the progression of the disease. Indeed, disclosure of risk status (by APOE4 genotype, a risk factor for Alzheimer's disease) significantly increases Alzheimer's-specific health-positive behavior changes, even when participants are specifically informed that no preventative behaviors are empirically supported (Chao et al., 2008). Further, a preclinical diagnosis for diseases that have no effective treatments, as in Alzheimer's disease, may increase the monitoring of symptoms. Diligent monitoring and screenings could enable earlier intervention once clinical symptoms develop. Decades of data following breast cancer screenings have demonstrated that women tend to increase their vigilance following a positive BRCA1 test –

with increased mammogram screenings (Botkin et al., 2003) and prophylactic mastectomy (Schrag et al., 1997) Well-informed participants are likely to be similarly vigilant in the context of preclinical brain disorders.

Preclinical detection can offer the opportunity to plan for the predicted disorder even if disease progression cannot be influenced. Here is another realm in which the treatment of preclinical brain disorders is unique, because the patient and their caregivers are often faced with an impending change in personality and behavior. The multidimensional contextualization of brain disorders often requires changes in the social environment, employment expectations, and independence. For example, an early diagnosis of ASD can allow a family to establish a home treatment plan or move the family to a location with strong support services (Sarrett and Rommelfanger, 2015). The definition of ASD (Pennington et al., 2014) and resources available for support services vary by locale, meaning relocating can substantially impact the child's and family's outcome. Similarly, awareness of developing schizophrenia or Alzheimer's disease can initiate a caregiver relationship, giving the patient and provider more time to prepare and plan. Pre-planning is crucial for caregivers, who often have to leave or transition their careers to care for their loved ones full-time.

4.3 Living with a preclinical diagnosis

If a patient chooses to be informed of their preclinical status, they face the risks of living with a preclinical brain disorder. Patients with psychosis anticipated that they would experience stigma in their interpersonal relationships and employment (Cechnicki et al., 2011), suggesting that a preclinical diagnosis could impact patients even if the diagnosis is kept confidential. The fear of anticipated stigma could prevent patients from sharing their diagnosis, leading to social isolation and preventing pre-disease planning and the establishment of a caregiver. The knowledge of one's status could also impair performance via stereotype threat. APOE4+ patients who were informed of their status performed worse on memory tests than those who were not informed (Lineweaver et al., 2014), and there is no evidence to suggest that reaction to a preclinical Alzheimer's disease diagnosis would be any different. In the case of ASD, in which parents receive their child's diagnosis, parents may begin to treat a preclinical ASD child differently even before social deficits arise (if they ever arise). The change in family dynamic could be detrimental to the family members diagnosed with ASD and those not diagnosed with the disorder.

If the patient chooses to disclose their status or is in a scenario where they are not given a decision (e.g. the results are automatically placed on their medical record), they become vulnerable to structural stigma and discrimination. In the United States, patients with preclinical diagnoses are not protected under the Americans with Disabilities Act because they have no current diagnosed disability. If information on preclinical status is made accessible, the law would need to be changed to afford protections. The U.S. Genetic Information Non-Discrimination Act can serve as a model for protecting patients from discrimination of preclinical status (2008), but no such legislation currently exists for biomarkers (Arias and Karlawish, 2014). The lack of standards surrounding how to treat individuals with a preclinical diagnosis leaves scientists and clinicians with the obligation to contribute to policy decisions, lest the science of preclinical detection outpace its legal and political frameworks.

The prospects of living with a preclinical diagnosis must include emergent and future technologies. In reality, all people are patients in waiting; all people are in a preclinical state for something. It is not simply that up to 36% of people ages 85 and above live with Alzheimer's disease (Alzheimer's Association, 2019). As predictive biomarkers emerge and the technology to detect them improves, every asymptomatic person will qualify for some preclinical diagnosis.

Therefore, research must understand and develop procedures on how to best live with a preclinical diagnosis in the social, legal, and personal realms, because those decisions will affect an increasingly large percentage of the population.

5. Communicating Risk

Much of the burden to ensure preclinical research and screening occur ethically will fall on the teams conducting the work. Relative risk is poorly understood on a conceptual level, so the practical effects of a patient's status must be described and discussed by the research/healthcare team. Teams directly involved in preclinical detection already recognize the difference between a statistically significant risk factor and a reason to change behavior. As an example, one team found that those in the top decile of risk profile scores (RPS) by genetic analysis had an odds ratio greater than 7 of developing schizophrenia. Although this is statistically significant and a substantial effect, the authors acknowledge that this information would have little real-world utility for patients and recommend against using the RPS as a predictive tool (Ripke et al., 2014). However, patients will have a right to know their status when similar tools are introduced into the clinical setting, which will require deliberate communication between the parties. Many individuals, scientists included, could feel that being 7-times more likely than the average person to develop schizophrenia makes the disorder inevitable, when in reality they have approximately a 7% chance of developing it in their lifetime (World Health Organization, 2001). High relative risk is easily interpreted as certainty, so the information must be presented in a contextualized manner as part of a larger discussion of what the diagnosis should mean for the patient.

Before disclosure of preclinical diagnoses becomes common practice, an agreement of *when* to disclose must be established. The relative value and risks associated with Type II (false negative) and Type I (false positive) errors will be a necessary part of preclinical detection, since biomarkers for developmental brain disorders are inherently probabilistic. In scenarios where health is not immediately compromised, high Type II error may be preferred over high Type I error, but these calculations would be different for every disorder, and every biomarker. Systematic research into public attitudes is the only way to determine the validity of that statement. An online survey by the Mayo clinic (Caselli et al., 2014) found that the majority of respondents from an Alzheimer's disease prevention registry would undergo biomarker testing if given the choice and that the results of the testing would influence positive lifestyle changes. However, a significant minority reported that a high-risk status would prompt them to 'seriously consider suicide'. This self-report is at odds with many reviews of health outcomes following the disclosure of risk status, which claim that the information tends to, at worst, induce transient anxiety or depression (Paulsen et al., 2013; Kim et al., 2015). In fact, patients were found to over-rate negative health outcomes and were more resilient than initially predicted. Even so, the extreme negative response of a subset of the population cannot be ignored. That, and the indeterminate effects of a preclinical diagnosis on stigma, employment, and healthcare highlight the need for risk disclosure to be integrated into psychological screening and counseling.

6. Recommendations

Preclinical detection of brain disorders, both for research and clinical purposes, impacts patients in unique ways. The introduction of detection technologies will likely not be controlled by the scientific community. Other groups have already noted that preclinical tests may be integrated into diagnoses by market and consumer pressures rather than by scientific consensus (Racine et al., 2017). Therefore, the introduction of these technologies cannot be passively integrated. Rather, standards for preclinical research and diagnoses must be established in anticipation of their adoption. These standards should be co-created with a variety of diverse stakeholders including patients, policy makers, scientists, and health care providers.

Even the practice of informed consent will need to be restructured in the context of preclinical detection. Longitudinal studies concerning brain disorders demand a custom consent protocol: a fully competent and autonomous patient at the beginning of a study may progress to a point of diminished capacity and autonomy over the course of the study. Standards of re-consenting a patient must be established and communicated to the patient (and applicable caregivers/powers of attorney) at time of enrollment.

Furthermore, the consent process must include all possible outcomes and results, not only those directly related to the brain disorder of primary interest. As the predictive power of preclinical biomarkers improves, more and more tests will have the potential to uncover incidental findings of a preclinical diagnosis. The search for biomarkers to diagnose a clinical disorder will likely include incidental and secondary findings, which have already permeated clinical settings with the increasing availability of genetic testing. Citing a duty to prevent the harm to patients, the American College of Medical Genetics and Genomics (ACMG) recommended that all clinical genomic sequencing be coupled with tests for a pre-determined list of pathogenic markers. More controversially, the ACMG recommends that the patient should not be given the opportunity to refuse either the test or the receipt of the results (Green et al., 2013). Their recommendation has caused many critics to cite a lack of respect for patient autonomy (Wolf et al., 2013), and other commissions have argued in favor for a patient's right to refuse (Presidential Commission for the Study of Bioethical Issues, 2013). Incidental findings may be inevitable in intensive screening, but the distress such findings can pose to patients is not inevitable. The consent process must inform the participant of known secondary findings and the possibility of incidental findings. The participants' preferences to know or not know should be integrated into the consent process, and neither decision should be a criterion for exclusion from the study or trial. After all, the place of incidental preclinical findings in a patient's life will change once they become stronger predictors of the development of a clinical state. Chneiweiss (2017) has argued that ethical use and disclosure of preclinical biomarkers is dependent on the use to the patient, and the utility of these markers are continually changing in this young field. Thus, guidelines for the primary or incidental detection of preclinical biomarkers must be regularly re-evaluated to accurately reflect the relationship between patient and preclinical diagnosis. A positive model for such guidelines is the policy of the Wellcome Trust, which, without mandating a specific course of action by research groups, requires a concrete and well-justified policy on the disclosure of incidental findings as a condition for funding (Wellcome Trust, 2014).

Clinicians and scientists would benefit from formal risk communication training in preparation for the results that will be disclosed to the participant. The qualities of effective communication cannot be assumed; the development of effective communication will require empirical research on how the public best understands and receives data on preclinical risk. In fact, the Presidential Commission for the Study of Bioethical Issues (2013) recommended that clinicians disclose absolute risk to patients instead of relative risk, even though the genetic tests discussed by the Commission directly informs relative risk. Such reports suggest that the most effective way to communicate relative risk is to translate it into a more intuitive metric. Here, partnerships with advocacy groups focused on specific diseases will be invaluable. Organizations such as Autism Speaks or the Alzheimer's Association form relationships between all parties affected by a brain condition—from the patients, to the caregivers, to the physicians, to the politicians. In addition, the advocacy work of these organizations has fostered trust in the community, which will be crucial to reach historically underserved populations (Dawson and Bernier, 2013; Cahill et al., 2015).

Deliberate public engagement will also improve the impact of a preclinical diagnosis. Patients prescribed antipsychotic medications were more likely to stay on their medication schedule and had improved health outcomes when they engaged in integrated pharmaceutical and non-pharmaceutical interventions, such as through community health partners (Zygmunt et al., 2002). Psychoeducational and family therapy programs, though common, had poorer outcomes than behavioral programs or case management (Zygmunt et al., 2002), showing how intuitive interventions are not always the most effective. Such multidimensional treatment approaches may be more effective than traditional pharmaceutical interventions for brain disorders with no current treatment. A multi-domain intervention, which included diet, exercise, cognitive training, and vascular risk monitoring, prevented cognitive decline in elderly people at risk of developing Alzheimer's disease to a greater extent than an intervention of basic health advice (Ngandu et al., 2015). This landmark study should serve as a reminder that preclinical research should not be restricted to the development of pharmaceuticals. Capitalizing on integrated and objectively measured strategies is imperative. Doing so will not only maximize therapeutic potential, but will facilitate public cooperation and trust.

It must be acknowledged that a significant potential for harm to patients may arise from existing legal standards, or lack thereof. Protections and rights of patients must be formalized before official preclinical diagnoses are put into practice. Considerations should include what information can be shared with the patient's health insurance provider and the patient's employer, as well as what protections should be put in place to guard against discrimination in the workplace.

As the ability to detect preclinical stages of disorders improves, standards must also contain protections against forced testing and disclosure of results. Given the loss of productivity associated with disorders like schizophrenia and Alzheimer's disease (Takizawa et al., 2015; Chong et al., 2016), screening employees for such risk could be an economic advantage for the employer. Again, examples from how individuals are protected from the maltreatment from their status of other biomarkers offer positive models. Nonsense mutations of monoamine oxidase A (MAOA) were one of the first genetic biomarkers associated with aggressive behavior and criminality (Brunner et al., 1993). Although the original team did not advocate the use of the MAOA marker to classify individuals as criminals or likely recidivists (Brunner, 1996), many worried that the MAOA biomarker would be used as a eugenic classification. Especially given the gene x environment interaction influencing the effect of MAOA status on behavior (Kim-Cohen et al., 2006), Baum and Savulescu (2013) argued ethical uses of MAOA status must focus on protection of the individual, not preemptive action taken against the individual. The same is true for individuals who carry a preclinical biomarker for a brain disorder; reactions to a preclinical diagnosis must focus on the mobilization of resources to prepare for the increased likelihood of a future clinical state. The use of biomarkers alone, be they preclinical biomarkers of Alzheimer's disease or the MAOA allele, are not sufficient to fully predict future behavior. Additionally, biomarkers alone are not sufficient to justify a change in how an individual is employed, in how an individual is treated, in how an individual's autonomy is recognized. Harm is inevitable if the scientific possibilities outpace the legal framework in which they reside. Therefore, it is incumbent upon the scientists involved in the research of preclinical detection of brain disorders to also be active advocates for patient-forward policy standards.

7. Conclusion

Brain disorders are becoming statistically more prevalent in a population that is living longer and that is less affected by communicable diseases (Borlongan et al., 2013; Effertz and Mann, 2013). We must recognize that everyone is a patient in waiting. All disorders are developmental in nature, and therefore many more disorders than those discussed above have discrete, if currently undiscovered, preclinical stages. Risk modification will be the future of healthcare as the science of preclinical detection progresses. A thorough investigation of best ethical practices is needed to manage the use of new tools in the clinic and beyond. Regulatory hurdles and public distrust can easily stymie or corrupt these advancements if scientists and clinicians fail to engage in conversations with policymakers and the wider public. Most importantly, we must recognize that the best practices will not be consistent across conditions or cultures. True appreciation for the risks of preclinical research requires the acknowledgement that the risks (be they stigma, impact on interpersonal relationships, or individual anxiety) are influenced by cultural norms. The need for empirical research to measure public attitudes is never more important than when identity and autonomy are directly impacted. We can maximize scientific advances and public acceptance by responding to, and not dictating, public views on the matter. Such a dialogue will help the scientific community protect patients before the harms of uninformed preclinical detection are inflicted upon them.

	Preclinical Biomarkers	**Prodromal Symptoms**	**Techniques for measuring markers or symptoms**
Autism	None identified	Decreased social engagement and eye focus (Jones and Klin, 2013)	Eye tracking (Klin et al., 2002), naturalistic observation (Baranek, 1999), structural brain scan (Hazlett et al., 2017)
Schizophrenia	None identified	Subclinical positive, negative, and cognitive symptoms (Goulding et al., 2013)	Clinical interview (Goulding et al., 2013),genomic analysis (Ripke et al., 2014)
Alzheimer's	Low CSF $A\beta_{1-42}$ with high CSF P-tau or T-tau, increased amyloid PET retention, autosomal dominant mutation (e.g. APP, PSEN1/2) (Jack et al., 2011; Dubois et al., 2014; Dubois et al., 2016)	Mild cognitive impairment	PET scan with injectable tracer, lumbar puncture, memory assessment (e.g. FCSRT) (Dubois et al., 2016)

Table 1. Recognized biomarkers, symptoms, and methods for detection. Alzheimer’s is the only disease of those discussed with recognized preclinical markers. Adapted from (Arias et al., 2018).

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