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Ethics of Early Intervention in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) research, treatment, and prevention focus increasingly on developing personalized interventions based on personal genetic, biological, phenotypic data, for early intervention (EI) to limit harm. This approach has much to recommend it, but important ethical and philosophical challenges follow that should be considered, which we analyze here. We argue that advancing understanding of the causes of AD undermines the clarity of the distinction between primary and secondary prevention. This makes it increasingly unclear how primary and secondary categories can be appealed to as the basis for making judgements about what interventions are permissible, and for distinguishing between acceptably vs unacceptably early points in life to intervene. Timely efforts at prevention are vital for limiting harm from AD and given the logic of EI is that, in presence of risk, earlier is better, one might assume that earliest is best. This may or may not be the case; however, the permissibility of intervening in different ways at different stages of life is complex and turns on numerous contextual factors. We consider the particular ethical implications of intervening at different points in the life course, presenting a valuable resource for negotiating clinical and policy implications of EI in AD.

INTRODUCTION

Alzheimer's disease (AD) research and treatment focus increasingly on developing better personalized interventions for prediction, diagnosis, and management, by analyzing personal biological and phenotypic data. AD is the most common form of dementia worldwide, and the World Health Organization[1] has recognized dementia as a "global public health priority". As the Lancet Commission (2017, p. 2673) states, "around 50 million people worldwide have dementia and this number is predicted to triple by 2050". Dementias in general and AD in particular impose a significant and growing health and economic cost (Winblad et al. 2016; Wimo et al. 2017). These factors provide the mandate for developing new strategies to reduce the impact of the disease and are driving a transformation in AD management (Crous-Bou et al. 2017; Livingston et al. 2017). The contemporary aim in AD management is to intervene early to reduce risk and impact, based on individuals' characteristics and susceptibilities. The need to consider the ethical ramifications of an EI approach is highlighted by a recent advance, which we use as a case study here, in

the development of a test for the presence of blood phosphorated p-tau 181 (p-p-tau 181) (Karikari et al. 2020) which, if reliable as a blood biomarker, will enable the diagnosis of AD earlier in life than at present and before the onset of symptoms, which would typically be the point at which individuals receive a diagnosis.

The EI approach has much to recommend it, but ethical and philosophical challenges follow that should be taken into consideration. We argue that an Early Intervention (EI) approach to AD undermines the distinction between primary and secondary prevention, and that this poses a risk for justice in the allocation of resources. In expanding the category of factors which may be understood as determinants of dementia, the delineation between what we understand as its causes (and thus targets of primary prevention) and its symptoms or effects in need of remediation (targets of secondary prevention) becomes unclear. This process is likely to be inevitable, given that a guiding principle of personalized medicine is that an increasingly granular understanding of the interplay of causes of a condition is the route by which disease etiology will be understood and effective treatments developed.

To specify the importance of this further, the undermining of the primary/secondary prevention category boundary is ethically significant in two respects: the first relates to evaluations of quality of life; the second is an epistemic challenge relating to resource allocation decisions.

First, in relation to quality of life, the general principle that it is better to prevent than to treat implies, at least without qualification, that primary prevention is *prima facie* necessarily preferable to secondary prevention. This is uncontroversial to the extent that we can agree it would be better to prevent people from experiencing the symptoms of disease than to attempt to merely ameliorate their impact or reduce their exacerbation. However, and for reasons which we deal with in more detail further on, this will lead to complex ethical dilemmas if it becomes possible in future to push back the earliest point of reliable identification or prediction via accurate prenatal tests for AD, including in particular for late onset, non-inherited forms of the disease, on the basis of which parents would be able to make a decision to terminate a pregnancy if they wish.

The second point, the epistemic challenge, follows from the first. Straightforwardly, it is important that we know how to distinguish between primary and secondary prevention interventions. If we do not have some way to delineate the two, then policy decisions about the allocation of resources to primary and secondary prevention will be done on the basis of incomplete, and thus potentially faulty, information. This is a serious risk which should be anticipated, and which we analyze in more detail later in the paper.

Finally, we argue that a consequence of an increasingly prevention-focused approach to AD management, and the blurring of the primary and secondary categories that this causes, may permit a radical medicalization starting early in life, if it becomes possible to better understand the genetic and biological risk of AD. Concerns about medicalization and the expansion of the medical domain in line with new therapeutic possibilities are not new or particular to AD. However, since the EI approach necessarily implies that earlier is better than later, the practical ethical ramifications of this for children and young people in particular should be properly scrutinized. Applying the lens of the p-tau 181 case study in particular, we will show how and why such tests undermine the stability of the primary/secondary prevention distinction and demonstrate why this is ethically significant for the reasons outlined so far.

CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

Most forms of dementia, including AD, are caused by neurodegenerative diseases (Querfurth and LaFerla 2010). Clinically, the onset of AD is often insidious and early symptoms frequently include difficulty recalling names, words and learning new information, general absent-mindedness and problems negotiating unfamiliar surroundings, alongside a reduction in social interactions. Memory problems are a key feature, but non-amnestic forms of dementia can also occur, albeit much less commonly. The disease is progressive by nature and leads to increasing memory loss and cognitive compromise, which is reflected in an ever more restricted vocabulary and the loss of more complex speech patterns. These cognitive symptoms are often accompanied by emotional changes including apathy, mood lability, a reduction in social skills, and on occasion psychotic symptoms emerge.

As the illness advances, speech becomes compromised and monosyllabic, psychotic symptoms become more prominent, as do behavioral disturbances and these changes are accompanied by a loss of bowel and bladder control, and restrictions in mobility. However, despite these seemingly obvious signs and symptoms, the diagnosis of AD can be difficult. Vascular etiology (vascular dementia), which may coexist with AD symptoms, poses a significant diagnostic challenge; as such, presentations early in the course of the illness can be difficult to characterize. This has prompted consideration of provisional diagnoses, such as 'probable AD', and channeled interest into examining the precursors of dementia such as mild cognitive impairment (MCI)—widely regarded as a prodromal phase of the illness (McKhann et al. 1984). The recent p-tau 181 blood biomarker study shows promise in being able to distinguish AD pathology from those associated with other dementias at the pre-symptomatic stage. As such, therefore, if the test is reliable it will assist in making diagnoses definitive rather than provisional.

Typically, the diagnosis of AD has been made definitively postmortem, although, as the case study explains, recent research suggests that p-tau 181 may be a reliable blood biomarker for confirming a diagnosis of AD before death. In AD, the brain is characterized by the accumulation of inter-neuronal amyloid (plaques) and intra-neuronal tau proteins (neurofibrillary tangles) that cumulatively aggregate as the illness progresses (Maccioni et al. 2004). The timing and onset of the illness is determined genetically and by age, and such familial AD that has dominant inheritance is referred to as *early-onset*. Clinical symptoms of this form of AD can emerge in individuals in

their late twenties through to their forties and fifties. In contrast, *late-onset* AD is more variable both in terms of its genetic loading, and its sensitivity to environmental influences such as alcohol intake, obesity and exercise. This form of AD is more capricious, and it is therefore also referred to as being *sporadic*.

Variability in the clinical picture of AD with respect to timing of onset and the manner in which signs and symptoms emerge has meant that there is a keen interest in identifying underlying biomarkers that can aid diagnosis, for example p-tau 181. For this reason, there are two broad definitions for AD: one for the purposes of research, the other for clinical practice. The latter requires the presence of dementia, in which there is a clear departure from the individual's prior cognitive state, such that there is evidence of cognitive compromise. Onset is usually insidious but in time it noticeably impacts upon functioning. Where functional impairment is modest or mild, the descriptor MCI is used to denote the same processes are occurring as in AD but that as, yet they have had less impact.

For research purposes, the criteria for AD extend to include biomarkers involving neuronal injury and neural pathophysiology. Elevated levels of tau proteins within cerebrospinal fluid (CSF), temporal and parietal lobe atrophy verified using structural imaging, and reduced temporo-parietal region uptake of glucose (evaluated using fluorodeoxyglucose PET) are used to determine neuronal injury. Regarding pathophysiology, evidence of amyloid on PET imaging or reduced CSF AB-42 levels are required (Selkoe and Hardy 2016). The more stringent and specific research criteria are not used in clinical practice, as their prognostic value remains unclear. However, the potential benefits of having biomarkers to identify, diagnose, and perhaps even monitor AD is indisputable, even though they inevitably raise significant ethical issues (Johnson and Karlawish 2015; Porteri et al. 2017).

CASE STUDY: BLOOD PHOSPHORATED TAU 181 AS A BIOMARKER FOR AD

A recent study by Karikari et al (2020) presents evidence that p-tau 181 may be an effective blood biomarker for Alzheimer's disease pathology at all stages of the disease, including, crucially, at the pre-symptomatic stage, which is especially pertinent to testing in younger people many years before onset. According to the study (Ibid., p. 423), the test *'identified Alzheimer's disease at the very early stages of disease and demonstrated high diagnostic accuracy'*, and *'could*

represent the first simple, practical, and scalable test for the diagnosis of Alzheimer's disease'. As such, if effective, this blood biomarker test represents an improvement on standard diagnostic CSF and PET tests, which are invasive, expensive, and not widely available. If the study evidence is reliable, the p-tau 181 blood test will also improve testing to differentiate between AD and other forms of dementias at earlier stages in the disease, which will help with ensuring appropriately targeted disease management.

Importantly for the purposes of this paper, the study suggests the p-tau 181 blood test can effectively identify AD pathology in younger people, given a mean age of 23 in one of the cohorts involved in the trial. This raises the realistic prospect of reliably diagnosing younger individuals with the disease—prior to the development of symptoms—so that they can decide whether to make lifestyle and treatment choices; however, it is important to note that these interventions offer no guarantee of preventing the progression of symptoms. Even if p-tau 181 proves to be an effective diagnosis tool, since there is still no cure or disease-modifying treatment for AD, the extent to which the diagnosis can be meaningfully acted upon is unclear. We will discuss the ethical ramifications of these issues over the rest of this paper.

RISK FACTORS AND DISEASE INDICATORS

Age is the most important risk factor for AD (Raji et al 2009). Declining physical and cognitive vitality is consistent with the advance of AD (Mucke 2009), and the probability that one will develop it is determined partly by one's individual biological and genetic constitution and partly by how this interacts—in a complex and as yet limited way (Van Cauwenberghe, Van Broeckhoven, and Sleegers 2016)—with environmental factors, consumption, exercise, and treatment choices (Scarmeas et al. 2009; Mayeux and Stern 2012). One's constitution may therefore be viewed as a causal component of the disease; and of course, control or elimination of *causes,* rather than symptoms, of a disease refers to primary prevention, rather than secondary prevention.

As Gullotta (1994) writes, primary prevention seeks to reduce the incidence of health problems in a population not yet showing signs of them, and as such operates on populations that can be described as 'healthy'. The difference from secondary prevention, therefore, turns on the clarity of the distinction between the presence of risk factors but the absence of formal indications for disease in the former, and

disease indications in the latter. But what does and does not count as a 'disease indicator'? And how does an indicator of disease differ from an indicator of risk *alone*? One straightforward answer might be that an indication of disease is a biomarker; however, a biomarker may *also* be an indicator of risk (Majkić-Singh 2011). More confusingly still, as Strimbu and Tavel (2010, p. 2) point out, the definition of a biomarker can be construed sufficiently broadly to, as the World Health Organization does, conceive them as:

> Almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction

Moreover, Dubois et al (2010, p. 1118) point out that the dual use of the term 'AD' to refer both to clinical manifestations *and* identifiable, but asymptomatic, neuropathological changes, is "a potential source of confusion, particularly in light of repeated reports that pathological changes ("Alzheimer's pathology") can exist without the concomitant clinical manifestations of AD". The p-tau 181 test underlines the complexity that this uncertainty has hitherto caused, insofar as part of the value of the test will follow from its ability to reveal the onset of AD before symptoms have occurred.

A complexity to which Blennow and Zetterberg (2010) allude follows from this; namely, that the precise causal role of biological, neurological, genetic and other factors may at any given point be unknown. For example, on the basis of their research into the genetics of AD, Bertram, Lill, and Tanzi (2010) conclude, in the case of the late onset variant of the disease, that much of the heritability for this variant has not yet been explained by known susceptibility genes. The authors cite Manolio et al (2009, p. 748)'s description of this as the '"dark matter" of Genome-Wide Association Studies, in the sense that "one is sure it exists, can detect its influence, but simply cannot see it (yet)"'. On this view the distinction between primary and secondary prevention is determined not by the *presence* of disease indicators, but whether we *happen to be able to identify them as such*. Given that dementia is progressive (Bird 2008), and the disease process begins long before one becomes symptomatic (Selkoe 2011), it has typically not been obvious how we are to say with certainty that what is indicated is *merely* risk rather than the disease process *actually* beginning. Tests such as p-tau 181 may change this. If so, they move further back in time the point at which we can say the disease process has begun, and by extension, therefore, the threshold between interventions deemed as primary or secondary prevention measures.

The moving of this threshold is important for several reasons. If a disease has both external and internal determinants, it is unclear how we are to reliably distinguish between what does and does not count as 'a cause' of its emergence and progression, and what is an indicator of risk alone. It is similarly unclear how we can reliably continue to distinguish between the two classes of prevention, given that the category of nominally secondary prevention targets will shrink as understanding of the causes of the disease increases, and the category of what are now primary prevention targets expands correspondingly.

This uncertainty entails several ethically significant challenges. First, it implies the labeling of larger proportions of the population 'at risk', which is likely to raise concerns over the medicalization of normal health. Second, there is a scientific challenge of not having a 'normal' population reference class in a paradigm characterized by personalized medicine and the granular analysis of individual health. Third, a public health challenge emerges if the categories of preventative intervention used to determine policies and practices of 'early' intervention become increasingly unclear. Fourth, in relation to EI specifically, there is a question about when in the life course it is permissibly early to intervene.

These consequence are all relevant given the hope that improved understanding of the causal basis of AD will enable more effective personalized medicine and lifestyle regimes (Gu et al. 2010; Bugg and Head 2011; Valls-Pedret et al. 2015), and given also that interventions to delay progression are currently heuristic because nothing as fundamental as a disease modifying or preventing drug has yet been developed (Citron 2010; Selkoe 2012), even if the p-tau 181 blood biomarker test proves to be a reliable early diagnostic tool. Having outlined why EI at the present moment threatens the clarity of the primary/secondary prevention boundary, we will now go on to analyze in more detail some of the ethical implications of this ambiguity.

ETHICAL ISSUES IN EARLY AND EARLIER INTERVENTION

Here we outline a range of salient ethical implications of early intervention at different stages in the life course, and which are driven by the ambiguous

delineation between primary and secondary prevention measure. The ethical implications encompass: differences between intervening before and after birth – for example between termination of pregnancy and the communication of risk information in childhood; differences between different kinds of interventions for improving and maintaining cognitive health—for example between lifestyle adjustments, pharmaceuticals, and brain training methods; and implications for identity over time. It is important to analyze the variety of ways in which efforts at prevention may take place and the points in life at which interventions can be made. Morally relevant considerations will differ due to these variables and the ethical status of intervening will therefore not be uniform. It is important to understand in detail the reasons for this lack of uniformity, such that a balanced judgment of different interventions across the life course can be arrived at. We will begin by considering how ethical considerations change across the life course.

From Late to Early Intervention

The EI approach becomes increasingly ethically contentious as we move from late to early life. For example, at the earliest point in the continuum, the possibility of accurate prenatal testing for non-familial forms of AD (Goldman 2012; Hercher et al. 2016) will bring eugenic concerns into the ethical debate about what kind of strategies for reducing the incidence of AD are permissible. If accurate prenatal genetic tests for not only inherited or early onset variants, but the more common late onset form of AD were to become available, it is probable that their use as a justification for terminating pregnancies would attract similar criticisms to those directed at currently available tests for conditions such as Down Syndrome (McCabe and McCabe 2011; Paul 2014). Even if one in general judges termination in such circumstances to be permissible, objections that termination on the basis of disease undermines solidarity, discriminates against people with diseases and disabilities, or is perniciously eugenic, should be taken seriously.

Parents in possession of the knowledge about the likelihood of their child eventually developing AD may or may not wish to terminate, but either way, the decision is unlikely to be straightforward. Most people will live many decades in good health before developing the disease, and this leads to a dilemma. Although AD typically occurs late in life, it causes severe harm when it does. With this in mind, how is the decision whether or not to terminate to be weighed? Is it better

to create people who are eventually very likely to experience serious harm from AD because this harm only occurs later in life? Or does the disproportionate harm that the disease causes, however eventual, justify termination? This latter question is redolent of debates concerning termination which have occurred about other conditions, such as congenital deafness or Down syndrome. In these conditions it has been argued among affected communities that termination should not be sought because the affected individuals, although affected from birth, have fulfilling lives of a quality that outweighs the deficits caused by their impairment. As such, the primary prevention of AD through accurate prenatal testing and termination requires a finely balanced ethical judgment, requiring careful thought given the contemporary prominence of the principle that we should favor prevention over treatment where possible.

Early Intervention, Primary and Secondary Prevention

Moving on to the epistemic challenge associated with preventing AD, we see that this also has ethically complex implications for EI or prevention efforts early in the life course. To return to the categorization ambiguity, if reliable blood biomarkers, or genetic markers or constellations thereof are identified it will be reasonable to construe them as targets of *either* primary *or* secondary prevention. They may be construed as primary prevention targets because they signify risk, but in the absence of symptoms which will only emerge some years or decades into the future (Naylor et al. 2012; Ryman et al. 2014). However, they may also be construed as secondary prevention targets, since if symptoms that will progress do begin to emerge, the markers identified may be causally implicated in that process (Bekris et al. 2010). Indeed, it is *because* they are implicated in disease etiology that, for example, genetic tests for Apolipoprotein E (APOE) (Taylor et al. 2010; Roberts, Christensen, and Green 2011) have been available since its causal role was uncovered, thus disaggregating it from the remaining "dark matter" (Maniolo et al. Ibid.) as a specific target for intervention. The same is true of the newly developed p-tau 181 blood biomarker test.

It is fair to note that this epistemic challenge is open to the objection that, while philosophically interesting, it is a distraction from the centrally important *ethical* priority of developing better interventions for reducing the harm done by AD. For example, Solomon et al (2014, p. 233) claim that "This

theoretical 'hair-splitting' is less relevant if prevention on any level is effective in practice". In other words, if we deem AD sufficiently harmful that we should try to eradicate it—however remote a target this may be at present—then determining whether or not the most successful interventions can be neatly categorized as primary or secondary prevention measures is subordinate to this imperative. We would argue, however, that it is not as straightforward as it appears to disaggregate the epistemic and moral concerns, in view of the consequences of the former for the latter.

Treatment or Prevention?

The first reason for this is quite straightforward: If we do not have some way to delineate the two, then policy decisions about the allocation of resources to primary and secondary prevention will be done on the basis of incomplete, and thus potentially faulty, information. The need to have a detailed understanding of how the two might be distinguished is reinforced by the p-tau 181 blood biomarker study, since it reminds us that medical understanding is not static and so must be recognized as revisable. As in other diseases, such as cancer, allocation decisions may be made partly on the basis of whether primary or secondary prevention should take priority in particular circumstances, and for particular populations of people affected or likely to be affected by AD, the difficulty in making the distinction poses problems for responsible policy-making and distributive justice.

The difficulty in making the distinction is also problematic in the contemporary era given the increasingly embedded norm that prevention is preferable to treatment, a claim to which domestic government[2] and National Health Service[3] policy attests in the UK[4], and is a goal of the World Health Organization[5] at the international level. The ability to observe this norm is compromised by an ambiguity concerning the extent to which secondary prevention truly *is* prevention. Since secondary prevention acts at an early stage of detectable disease, it can be construed as a form of *treatment* insofar as it seeks to arrest the exacerbation of symptoms rather than to eliminate the cause of disease and prevent its occurrence. As such, if the *prima facie* principle of prevention being preferable to treatment is correct, it is

unclear why we should not always prioritize primary over secondary prevention measures, since the former category is not vulnerable to the dual interpretation of the latter. When combined with the epistemic uncertainty outlined so far about how to distinguish between the two categories, this poses a challenge for fair policy development and resource allocation decision-making.

Moreover, and to reinforce the continuity between the epistemic and ethical challenges, the potential introduction of an intervention such as accurate prenatal testing for AD as a basis for termination of pregnancy *is* ethically significant, irrespective of whether or not one is nominally in favor of it as a reproductive choice. Decisions to terminate on this basis are likely to be riven with uncertainty, even if the test could predict with high accuracy that an embryo is very likely to become a person who develops late onset, non-inherited AD. Even if a test could indicate that person X is highly likely to develop AD assuming average measures in terms of consumption choices, exercise, exposure to pollution, and so on, it would present further dilemmas. On the basis of this information, and in the absence of disease-modifying or curative treatments, X would have to live in a highly regulated way throughout life, avoiding wherever possible situations that confer risk and with certain life choices probably precluded from childhood onwards. In the face of such knowledge, therefore, parents would be faced with choosing between either terminating the pregnancy to avoid the eventual harm that would be likely to occur, or continuing to term knowing that the child will have to live in a restricted way throughout their life. As such, it is not only inherited or early onset variants of AD to whom ethically complex decisions will pertain, were it to become possible to test accurately for risk of developing the disease later in life.

Finally, here, it is important to emphasize *why* this ethical challenge is important, given that such testing is not yet possible. It could be objected, since such testing is still only theoretically possible, that the ethical dilemmas involved represent a science fiction scenario and so do not warrant serious consideration. However, this objection is short-sighted, given that the motivation of government funding, industry and medical research is clearly toward early and earlier testing for risk of AD. The purported value of the p-tau 181 blood biomarker test is grounded in its capacity to push back earlier in life the point at which testing for the disease can be done. This too was a science 'fiction' until the point at which the test was

developed, and we cannot assume that further diagnostic and predictive means will remain as fictions in perpetuity and therefore consideration of the relevant ethical implications is not irrelevant or unworthy of advance consideration.

Ethical Trade-Offs in Early Disclosure

Moving on from this issue similarly ethically significant is the tradeoff between the benefit to be derived from potentially delaying or avoiding the onset of AD through lifestyle and treatment choices made early in life, and the psychological and emotional distress that may be caused by receiving distressing but uncertain risk information before adulthood, if early intervention programmes for AD are routinely provided. Ethical dilemmas extend beyond the permissibility of the obviously contentious matter of pre-natal termination, into considerations relating to early-life interventions, including the issue of medicalization.

When considering the possible range of early life interventions, we might ask whether, for instance, there is an important ethical distinction between recommending preventive medication on one hand, and brain training (Gates et al. 2011; Gates and Valenzuela 2010) or lifestyle adjustments such as exercise that conduce to cognitive health on the other (Gregory, Parker, and Thompson 2012; Balsamo et al. 2013). A straightforward observation might be that there is at least a *categorical* difference insofar as the first requires the ingestion of a pharmacological agent, whereas the latter interventions requires only the application of one's existing capacities for consolidating one's health. Whether there is an *ethical* difference between these, however, would depend on whether on deems the pharmacological 'medicalization' of normal health as pernicious compared to more 'natural' methods (Bostrom and Sandberg 2009). Arguments in both directions may in turn follow from underlying assumptions, beliefs, or prejudices which may or may not have grounds for justification. Irrespective of which way one falls on this issue, therefore, the ethical status of *different kinds* of preventative after-birth interventions is not necessarily uniform.

Age, Capacity, and Identity

The age at which one makes choices about one's treatment or lifestyle may also influence the ethical conclusions that one reaches. Age is a factor associated with mental capacity (Jones 2013), which typically plateaus between late adolescence or early adulthood and some point in old age. In the UK context, particular ages, such as 16 and 18—namely, the legal age of consent to treatment and the attainment of adulthood[6] respectively (Palmer and Gillespie 2014)—are nominally assumed to have significance with respect to capacity. However, since age and maturity are not absolutely consistent, the age at which one *actually* attains capacity varies (Havenga and Temane 2016), as does the age at which one loses it. We might be uncertain, therefore, about the extent to which age *per se* is relevant to capacity in terms of how decisions pertaining to disclosure of personal risk information and actions that might follow from that information should be managed (Noroozi, Singh, and Fazel 2018) (Noroozi, Singh, and Fazel 2018) As such, it is not only the categorical difference between pre- and post-birth that has a bearing on the point at which intervention can or cannot be justified.

Age-related ethical challenges do not stop there. Even if the matter of capacity at a given point in life were settled, there are also deep empirical and philosophical uncertainties concerning the nature of personal identity over time (Shoemaker 2007; Swinburne 2019).

Assuming that one first commits to the existence of a continuous personal identity over time - a commitment that is more contentious than it first appears (Merricks 2001)—the transition from childhood into adulthood inevitably affects some of the choices that one makes. It is beyond the scope of this paper to enter into discussion of the complex and considerable bioethics literature on personal identity (Glover, 1988; De Grazia, 2005; Shoemaker, 2003). Suffice it to say that, whether or not one holds that identity can persist over time, given that preferences and values often fluctuate through development and with ageing, it cannot be assumed that decisions taken early in life for the benefit of the projected individual in the future are the same decisions that the future individual would in fact make. Given that decisions made in childhood or adolescence may have irreversible consequences, it is therefore important that the gravity of early life interventions are taken sufficiently seriously when options for intervening are being considered. In particular, parents have a responsibility toward their children and are obliged to act in their best interests as far as they can.

The question of obligation and responsibility in light of positive test findings thus raises additional ethical dilemmas. For instance, it is not obvious that

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[6]Excluding Scotland, where adulthood is also legally reached at 16.

just because one receives positive risk information for AD, one is therefore obliged to take action for reducing the risk. Stipulating an obligation of this kind would be contrary to norms of healthcare practice insofar as it would undermine the protection of patient self-determination. It could also be construed as harmfully coercive if to do so conflicted with the individual's wishes in the absence of any reason to think that their capacity is compromised (Wertheimer 1993; Arnold 2001). Notwithstanding changes to norms that prioritize individual self-determination over the collective good a discourse exists debating the integrity of an *informal* principle that suggests individuals bear an obligation to take greater personal responsibility for their own health (Brown 2013) in the name of the collective good (Buyx 2008; Feiring 2008).

The risk of this informal obligation exerting pressure is made more acute and immediate if tools such as the p-tau 181 blood biomarker test prove to be reliable and can identify AD pathology early in life. Early intervention measures may, therefore, reveal a tension between the rights to which individual citizens are entitled and the obligations that they bear to society. Even if one concludes that individuals *are* obliged, for whatever reason, to engage in risk reduction or prevention, this still does not specify whether there is a threshold beyond which one is obliged, and if so what this threshold might be. A 1% risk is still a risk, but it is negligible, whereas even a risk as low as 25% is considerable. Questions remain, therefore, about where any obligation to attempt prevention would begin.

Disease and Neurodiversity

It is worth highlighting briefly here before moving toward our conclusions one way in which AD is different from other kinds of neurological conditions in which some would consider early intervention to be worthwhile, such as autism (Boyd et al. 2010; Warren et al 2011) and psychosis (Bird et al. 2010; Marshall and John 2011). These conditions typically manifest much earlier in life than AD and, while they can be debilitating, an advocacy movement exists which argues that individuals can live satisfying lives and flourish with conditions such as these (Nicolaidis 2012; Austin and Pisano 2017). Indeed, it has been suggested that autism, and some 'symptoms' of psychosis such as voice hearing, should not be regarded as diseases, but as examples of 'neurodiversity' (Mcgee 2012; Runswick-Cole 2014). By contrast, although

people in general live many decades before suffering the impairments associated with their AD risk, by comparison to the body of research and advocacy that exists in the autism community, and, notwithstanding some notable analyses (Carlson 2016; Shakespeare, Zeilig, and Mittler 2019) the same kinds of argument in favor of reframing the condition as a set of valued differences rather than a disorder are largely absent.

Having gone into some detail about specific ethical implications of an EI approach to AD, in the next section we make some general and final remarks to reinforce why this is a pressing matter that we should anticipate. Before we conclude, it is important to tie together the analytic strands that we have laid out in the preceding analysis to emphasize the ethical significance for individuals and parents of EI options in the AD context as the trajectory of research, understanding, and policy moves in this direction, and if this trajectory makes ambiguous the distinction between primary and secondary prevention.

EMPHASIZING THE ETHICAL SIGNIFICANCE OF EARLY INTERVENTION IN ALZHEIMER'S DISEASE

The significance of growing up with a diagnosis is that younger people who test positive for diagnostically reliable AD pathology earlier in life must live with the potentially traumatizing knowledge that they *already have* a biomarker of a so far irreversible degenerative disease—albeit one that may not yet be symptomatic but which will become symptomatic in future—and the impact upon their identity and wellbeing that this can cause. This knowledge moves them into the category of the already diseased; that is to say, those for whom secondary, rather than primary prevention measures are appropriate. It is unclear in such instances whether having the knowledge is necessarily preferable, simply because it is acquired earlier in life than it hitherto would have been. Indeed, in the absence of effective therapy, a diagnosis early in life and the labeling that follows from it may be stigmatizing, and disabling in terms of the restrictions that the knowledge is likely to impose for affected individuals. It is true, in a sense, that all of the questions which arise in the EI context and enumerated here are morally important *irrespective* of how cleanly they do or do not map on to nominal definitions of primary and secondary prevention. However, their moral importance cannot be circumvented simply by insisting that if a treatment is effective it defuses *all* ethical debate, because what ought to be done will be

influenced by *how* effective the treatment is. Indeed, it is fair to say that if a 100% effective and safe preventative 'cure' for AD were developed, it would be equally fair to argue that it is irresponsible not to take it. Since uncertainty about the outcome would be eliminated in this instance, the basis on which one might defend not trying to prevent it because one might not develop it anyway would be undermined. Given the complexity of AD, its causes, and how much is still yet to be understood, however, this scenario is unlikely at present. As such, it is inevitable that ethical deliberation will be primarily grounded in what ought to be done on the basis of how effective a given treatment happens to be.

As we have seen, the particular intersection of AD and the principles of EI reveals the distinction between primary and secondary prevention to be more tenuous than it appears. Advances in knowledge in a disease such as AD might threaten the clarity of the distinction between categories of prevention; this means we should rethink our assumptions about how to categorize prevention at different stages of health and what we regard as permissible with respect to them. This is ethically important not only for philosophical reasons already outlined, but also because these categories have a bearing on external concerns about distributive justice. For example, it would be ethically troublesome if it turned out that the distinction were heavily relied upon in resource allocation decisions, for example in terms of differential funding for primary and secondary prevention interventions, or in access to treatments nominally identified as falling into one category rather than the other. Problems of classification in instances such as this reinforce the practical ethical consequences that can follow from the epistemic uncertainties that we have identified in the preceding analysis.

CONCLUSION

If the logic of EI is that, in the presence of risk, earlier is better, then without proper scrutiny as to what the ethical tradeoffs will be of different modes of intervention at different stages of life, one might assume that earliest must be best. However, this depends on what the attendant facts and consequences are of particular interventions. For example, whether earliest *is in fact* best will, when thinking about choices at the earliest point in life, turn on the moral permissibility of termination on the basis of positive prenatal genetic testing (assuming that accurate predictive testing of this kind becomes available). Similarly, whether or not information should be communicated to children and young people about a high risk of developing AD, and the choice about whether to make use of diagnostic tools such as the p-tau 181 test, depends on several factors, including the accuracy of the information; the likely effectiveness of interventions recommended, especially given the current absence of disease-modifying treatments; the impact that a potential foreclosing of options and life choices may have on the individual now and in the future; and how the relative benefit of possibly, but not definitely, avoiding or delaying the onset of AD in future by steps taken now weighs against the benefit of enjoying unrestricted choices in the present.

In both cases the argument for an EI approach to AD can be construed as defending a radical medicalization from early in life. However, although medicalization often carries negative connotations, it cannot be appealed to as *necessarily* ethically problematic (Parens 2013). Rather, whether medicalization in the context of AD is or is not ethically permissible, desirable, or necessary, can only be determined by the values we attach to the various consequences of doing so. A challenge for being able to determine this at present follows from the state of our knowledge of AD, its causes, and ways to effectively mitigate or prevent its effects. Consequently, more evidence is required for the effectiveness of EI strategies to intervene in AD. Given the scale of the consequences for individuals that may result from intervening early in their lives, not least in view of the practical ramifications of uncovering new, more readily testable and reliable biomarkers such as reported in the p-tau 181 study, investment into the production of such evidence is required, in spite of concerns about EI being understood as creeping medicalization in the AD context.

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