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Ethical and social implications of using predictive modeling for Alzheimer´s disease prevention: a systematic literature review

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Abstract

The therapeutic paradigm in Alzheimer's disease (AD) is shifting from symptoms management towards prevention goals. Secondary prevention requires the identification of individuals without clinical symptoms of AD, yet "at-risk" of developing Alzheimer's dementia in the future, and thus, the use of predictive modeling.

The objective of this study was to review the ethical concerns and social implications generated by this new approach.

We conducted a systematic literature review in Medline, Embase, PsycInfo, and Scopus, and complemented it with a gray literature search between March and July 2018. Then we analyzed data qualitatively using a thematic analysis technique.

We identified thirty-one ethical issues and social concerns corresponding to eight ethical principles: (i) Respect for autonomy, (ii) Beneficence, (iii) Non-maleficence, (iv) Equality, Justice and diversity, (v) Identity and stigma, (vi) Privacy, (vii) Accountability, transparency and professionalism, and (viii) Uncertainty avoidance. Much of the literature sees the discovery of disease-modifying treatment as a necessary and sufficient condition to justify AD risk assessment, overlooking future challenges in providing equitable access to it, establishing long-term treatment outcomes and social consequences of this approach, e.g. medicalization. The ethical/social issues associated specifically with predictive models, such as the adequate predictive power and reliability, infrastructural requirements, data privacy, potential for personalized medicine in AD and limiting access to future AD treatment based on risk stratification, were covered scarcely.

Therefore, the ethical discussion needs to advance to reflect recent scientific developments and guide clinical practice now and in the future, so that necessary safeguards are implemented for large-scale AD secondary prevention.

Word count: 249/250

Keywords: dementia, early diagnosis, early intervention, prodromal symptoms, secondary prevention, biomedical ethics, qualitative research

INTRODUCTION

Alzheimer's Disease (AD) is the cause of 70% of all dementias [1], characterized by the combination of cognitive, behavioral and functional decline, leading to loss of autonomy. AD represents a significant public health challenge worldwide. The disease course is understood as a continuum from the preclinical stage without cognitive symptoms, to Mild Cognitive Impairment due to AD (MCI) and then dementia due to AD. Knowledge of the pathophysiology of AD has improved over the last decade, bringing about a deeper (albeit not conclusive) knowledge of genetic predisposition, identification of biomarkers (e.g., amyloid-β (Aβ) plaques in the brain or tau protein in cerebrospinal fluid) as well as new insights about their interaction with protective or disease-promoting factors [2–4]. In turn, these genetic, molecular and environmental risk factors, or the subjective perception of declining cognitive capacities have been found useful to identify cognitively unimpaired individuals at higher risk of developing MCI due to AD and later on dementia due to AD [5–7]. Consequently, the therapeutic paradigm of AD has recently shifted from symptoms management in individuals diagnosed with MCI or dementia based on their clinical symptoms, to secondary prevention goals targeting "at-risk" individuals and aiming at modifying the natural course of the disease. Contributing to this shift are recent drug development programs testing earlier in disease course compounds that previously failed in clinical trials (RCTs) on participants with MCI or dementia [8], in a hope that they can be efficacious if used earlier in the disease course, even at preclinical stages of AD [9]. Recent claims that aducanumab, an anti-Aβ immunotherapy, improves cognition in patients with MCI or mild AD, lends some credibility to this approach.

In the research setting, participants are enrolled to the clinical trials testing preventive treatments only if they have elevated AD biomarkers or genetic predispositions (cf. clinicaltirals.gov identifiers NCT02008357, NCT01931566). However, even such patients

have a fairly low probability of developing AD in the future. Predictive modeling, i.e., the use of patients' data and of statistical models to estimate the likelihood of future outcomes, based on historical data [10], can help to produce a more accurate assessment of the probability of conversion from being cognitively unimpaired to MCI or dementia within a certain timeframe. Data used in such models: individuals' demographics (e.g. age, sex, level of education), genetic markers (e.g. APOE4), and comorbidities (e.g. cardiovascular diseases) as well as longitudinally captured brain imagining metrics (e.g. PET scans to establish Aβ status) and results of cognitive tests can, can typically be found in clinical registries from memory clinics. Even though as of today the applications of such models are mostly in research settings, some clinics offer AD biomarker testing to their patients, followed by non-pharmaceutical intervention, e.g. lifestyle changes, cognitive rehabilitation, etc. In a future, aspirational scenario, predictive modeling could be applied in combination with a preventive treatment (currently not available), e.g. to identify patients with high risk of developing clinical symptoms of AD or patients likely to benefit most from the therapy.

A predictive model could also be developed based on minimal sets of demographic and clinical information. Such model could be used in a hypothetical scenario for broad (e.g. population) screening aiming to crudely sift out from a general population individuals who might have an increased risk of developing AD in the future, so that these individuals could undergo further investigation using brain imagining, and other biomarker or genetic analyses. Such new therapeutic paradigm in AD raises numerous ethical concerns and may have various social implications. Some of these concerns are typical for preventive medicine in general, yet at the core of the problem is AD's specific setting – the need to intervene years or even decades before the onset of any cognitive, behavioral or functional decline [11] without a certainty that an individual would ever develop clinical symptoms of AD, while the long-term consequences of these interventions are not yet fully understood. Uncertainty about the

long-term consequences of future preventive AD treatment is due to the long natural history of AD which makes it impossible to evaluate in clinical trials, currently lasting up to 5 years in AD, all its clinical consequences. Likewise, the clinical trials will not be sufficient to fully appreciate the long-term societal consequences of preventive intervention, critical also from the perspective of drug reimbursement, due to the limited length of follow-up, narrow choice of endpoints, and stringent inclusion criteria. This is another context where predictive modeling can and likely will be applied to remedy the knowledge gaps, e.g. through models bridging between strictly clinical trial endpoints (like neuropsychological assessment) and societally relevant outcomes (like institutionalization). Yet, predictive modeling and the entire discipline of predictive medicine enabled by the technological and computational developments in the recent decades raises further ethical concerns and social implications. A lively scientific debate about the ethical aspects of recruitment of pre-symptomatic individuals to clinical trials and observational studies has already been taking place in the recent years [12]. As AD prevention efforts will need to target a large number of people in order to be impactful this debate will intensify. As soon as an efficacious preventive treatment is developed, a sense of urgency will arise to provide Disease-Modifying Treatment (DMT) [13] to aging populations, to prevent public health crisis and the associated soaring burden of care.

OBJECTIVES

The objective of the present study was to systematically review and discuss the ethical concerns and social implications raised by the use of predictive modeling in the setting of secondary prevention of AD. We focused on the types of arguments with particular relevance for current and future, anticipated or aspirational clinical practice.

Here, we defined secondary prevention as targeting people “at risk” of Alzheimer’s dementia

with an intervention aiming to prevent or delay the onset of clinical symptoms [14,15]; and predictive modeling as the use of data from multiple individual subjects in statistical models to identify the likelihood of future outcomes—including patient-level outcomes—based on historical data [10].

Our specific research questions were identified through a preliminary, targeted literature search [16] and include the following:

1. What are the ethical concerns and social implications associated with
    a. Selection of individuals for assessment of the risk of developing clinical symptoms of AD via predictive modeling, from a general population or population with known risk factors?
    b. The disclosure of individual's risk of developing AD clinical symptoms assessed using predictive modeling?
    c. Preconditioning of access to AD preventive treatment, based on the predictive modeling, e.g. by selecting patients at high risk (in a future, aspirational scenario)?
    d. Assessment of the benefit-to-risk from AD preventive treatment administered at the preclinical stage, made using predictive modeling?
2. What are the broader, population-level ethical concerns and social implications of using predictive modeling tools in the setting of secondary AD prevention?

METHODS

Definitions

Whenever we refer to MCI or dementia we mean MCI due to AD, and dementia due to AD. The term "at risk of AD" refers here to being cognitively unimpaired but having an elevated risk of developing clinical symptoms of AD in the future, regardless of how this elevated risk

was established (e.g. using genetic or biomarker analysis, or using an aggregation of risk factors from multiple data domains). “Preclinical AD” refers to cognitively unimpaired individuals with established AD biomarker. Whenever we use the term “preventive treatment” we mean the future, aspirational drug targeting AD, used before AD clinical symptoms are developed.

Protocol development

The study protocol was prepared according to the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols 2015 (PRISMA-P) [17,18], registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42018092205) on April 6th, 2018 and published [19]. The completed PRISMA-P checklist is provided in the Supplementary table 1.

Search methods

A comprehensive, systematic literature search was conducted between May and July 2018. The literature was retrieved from the Embase/Medline Daily, Scopus and PsycINFO between 28th and 31st of May, 2018 including coverage from 2007 until the search date. Additionally, a gray literature search was performed within pre-defined websites of relevant non-governmental organizations and professional associations, and using a generic Google search engine, where the first 10 pages of results were reviewed for potentially relevant entries. The full electronic search strategy is provided in the Supplementary table 2.

Study selection

The systematic literature search followed the SPICE framework (Setting, Perspective, Intervention, Comparison, Evaluation) [20]. Included in the analysis were studies discussing ethical concerns or social implications, both from individual and societal perspective, both of using predictive modeling methods (statistical algorithms) and source data (e.g.

demographics, genetic data, imaging data, cerebrospinal fluid examination, etc.) as a component of secondary AD prevention. Studies were included if discussing preclinical AD, including those with subjective memory complaint/cognitive impairment but without MCI diagnosis. We included studies reporting on the results of research on humans (basic, clinical, social, reviews/meta-analyses, observational, randomized controlled trials), including conference abstracts, editorials, commentaries, guidelines, discussion and position papers, books and book chapters published in English, French or German from the year 2007 onwards. The choice of this time span reflects the fact that secondary prevention is a recent therapeutic strategy against AD. Details of the study selection criteria are presented in Table 1.

[Table 1 about here]

The retrieved abstracts were independently assessed by two reviewers and disagreements were adjudicated by a third reviewer. Reviewers had a possibility to exclude not eligible studies based on a review of the full-text versions prior to the extraction process.

Data extraction

Data were extracted from the eligible studies by single reviewers. The extraction was performed using a semi-structured extraction sheet where textual content extracted by all reviewers was uploaded in real time into an online spreadsheet for further qualitative data analysis. Text fragments were extracted according to the pre-specified research questions, aforementioned in the introduction of this paper, with a checklist of ethical concerns or social implications known to appear in this context. This checklist was derived from a seed of four studies [21–24] selected for this purpose by one reviewer and a bioethicist independent to this study. Lastly, for each of the research questions, open-ended text boxes were added to allow for capturing all novel themes, arguments, and considerations that were not initially included

in the structured checklist. The extraction sheet development process is described in more detail in the systematic review protocol [19].

Data analysis

Extracted data were analyzed qualitatively using a thematic analysis approach [25,26] defined as "a method for identifying, analyzing, and reporting patterns (themes) within data which minimally organizes and describes (your) data set in (rich) detail but also interprets various aspects of the research topic" [25]. The theme is defined as "a repeated pattern of meaning, capturing something important about the data in relation to the research question, and representing some level of patterned response or meaning within the data set" [25]. In characterizing salient ethical arguments the focus was on the claims being made and the arguments supporting them, not on quantitative assessment of the number of times a given claim appears in the literature. Therefore, the frequency was not treated as a measure of importance. The research questions of this study defined the highest level themes which were further broken down into the lowest level of ethical and social considerations. In order to make sure that complex ethical arguments were understood in context, full-text papers were revisited during the iterative analytic process and reviewers were encouraged to use memos liberally during extraction and analysis. Both pre-specified and newly identified ethical and social considerations were then classified as either ethical concern or social implication, and grouped into themes. The connections and interdependencies between the themes were investigated. While the analysis relied upon self-nomination of ethical relevance by a reviewer, the grouping into ethical themes was matched with the additional mapping of the ethical principles establishing the perceived ethical relevance of each theme to the issue of predictive modeling. These principles were drawn from background literature in medical and public health ethics, including the four core principles of 'principlism' in biomedical ethics [27].

Risk of bias

One potential bias to a literature review is to treat what is most commonly reported as the most important. This bias is mitigated by the qualitative character of the present study, striving to understand a wide spectrum of the ethical and social concerns and disregarding their frequency in the literature. However, a potential inter-reviewer heterogeneity when different reviewers appraise manuscripts and documents in a different manner could result in some ethical arguments being missed or misinterpreted. To mitigate this bias, the team of reviewers participated in a face-to-face workshop on April 28th, 2018 in Barcelona, during which the research objective, strategy, and extraction tools were thoroughly discussed and reviewed when needed. Further to that, the reviewers come from different backgrounds, including sociologist, clinical psychiatrist, psychologist, market access professionals specializing in AD, a pharmacist and market access professional, and a mathematician/statistical modeler. Finally, the results could be affected by a publication bias.

RESULTS

Study selection

The systematic literature search yielded in total 180 citations, 154 in bibliographic databases including Embase/Medline, PsycInfo, and SCOPUS and 26 through a manual search conducted in Google. After removal of duplicates, 152 abstracts were screened against the inclusion criteria and 92 were excluded at this stage. After full text screening 12 additional publications were excluded. Reasons for exclusions are listed in Figure 1. In total, 48 publications were retained.

[Figure 1 about here]

Study characteristics

Of the forty-eight retained publications, thirty-two were journal articles with the majority of them coming either from medicine/gerontology (thirteen out of thirty-two) or interdisciplinary domain (twelve out of thirty-two). Four articles came from psychiatry or neuroscience field, and the remaining were published in social science or ethics journals. Seven further publications were either conference abstracts, proceedings or presentations, six were reports and three were books or book chapters.

Results of the individual studies

Table 2 summarizes the ethical concerns and social implication identified in the literature, structured along the research questions. Table 3 shows the matching of ethical concerns and social implication to one or more ethical principles.

[Table 2 about here]

[Table 3 about here]

Selection of a population for risk assessment via predictive modeling

Who should have their AD risk assessed is one of the critical questions in the ethical debate around AD prevention. One approach could be population screening, e.g. screening everybody after a certain age, yet such an intervention might lead to "turning everyone into patients" [12,21,23,24,28–33] and excessive operational burden for healthcare systems. Alternatively, model-based, precise assessment of AD risk could be made only among those with known risk factors for AD. While these two approaches belong to the classic arsenal of public health prevention, another unique concept identified in the literature was "screening whoever wants to be screened" [34] yet not without a question whether access to screening should be limited to individuals assessed beforehand as emotionally capable of eventually learning their risk status (e.g. not prone to depression). This concept is best summarized as

"screening before screening" [12,21,28,31,35–37]. Voluntary access to screening can be defended on pragmatic grounds by the fact that commercial genetic testing for AD is already available and will most likely come into large demand as soon as DMT is developed [34,38]. Policymakers must ensure that healthcare and social systems are prepared in terms of implementation of laws safeguarding a growing number of patients, their data and their interests and that professional and social policies are put in place to not only treat but also advise and educate them [28,31,35,39–45].

Several ethical themes speak against assessing the risk of AD. The most prominent of them is the current lack of DMT rendering risk assessment not actionable [21,22,46–54,24,28,32,33,35,37,40,43] and potentially even harmful, e.g. when side effects of invasive biomarker testing are considered [30,41] or the threat of overdiagnosis [4,12,33,37,40–43,54,21,23,24,28–32] and competing risks are taken into account [37,40,42,54]. The issue of competing risks is particularly valid in the AD setting, where at-risk or preclinical stage might span decades and where the elderly patient population might be prone to other age-related diseases. Further reservations against AD risk testing are: lack of adequate tests with sufficient predictive power to provide a trustworthy risk assessment [21,30,33,38,42,54], lack of social consensus as to what predictive power could be considered sufficient [21,38], and uncertainty, whether the presence of Aβ plaques is causally associated with AD [37,40,42]. The latter argument is not relevant, though, in the predictive modeling setting, where co-occurrence can be sufficient to predict future outcomes.

Disclosure of individual risk assessed using predictive modeling

Considerations around disclosure practices do not differ substantially depending on whether they are based on genetic, biomarker or imaging assessment, with an exception of the specific discussion on familial, early onset AD. Particularly relevant in this context of people with high risk are arguments in favor of disclosure due to the psychological benefits of resolving

patient's uncertainty of their AD risk [37,39,53] and possibilities for future planning [4,12,57,58,30,31,35,37,43,48,55,56]. Ethical considerations depend in turn to a large extent upon whether the disclosure is made in research setting in the absence of DMT vs. in hypothetical clinical setting where DMT is available. In the latter case, there might even be an ethical obligation for disclosure [4,31]. The governing ethical principle here is a postulate that the diagnosis should provide a patient with a benefit that overweighs the risks. Some papers, however, consider benefit much broader than access to treatment, pointing rather to the need of establishing whether a risk assessment brings clinically meaningful information [4,31], considering patient's individual situation, including the availability of support [39,40,59] and their level of willingness to know their risk status, as it might mediate the level of benefit from the diagnosis [4,35,40,58].

On the other hand, major groups of arguments against disclosure address psychological harms associated with the remaining, post-testing uncertainty of the positive risk assessment until symptoms occur [12,30,36,37,40,53] and even without certainty whether they will occur, given the possibility of a false-positive diagnosis [38,53]. The ethical and social ramifications of a false-negative diagnosis are not specifically discussed in the literature. A very prominent theme in the literature stresses the risk of discrimination of people with high risk of developing AD symptoms within the workplace, healthcare system and society overall [21,22,58,28,39,40,44,45,49,55,57] which might lead to their distress [4,37,40,43,49,56] and potentially even objective, realistic limitation in how they perform in their daily life [12,30]. AD risk assessment can bring about negative consequences not only to the patient, but to his or her relatives and significant others, as they might become anxious about their own risk [39,40] or about the upcoming challenges of taking the role of a supporter or carer [39,40].

Accurately communicating AD risk assessment to patients is considered challenging given the complexity of the issue, the differences between patients [28,39,53], e.g. in terms of their

level of understanding of the disease and the uncertainty of preclinical risk assessment, level of agency and support, individual predispositions for depression; as well as unique statistical properties of particular methods which are used to make such a prognosis[38,58].

Treatment: preconditioning access to treatment and assessing benefit from it using predictive modeling

The relationship between the access to screening and to the treatment is reciprocal, meaning that the recommendation for screening is often preconditioned on the availability of DMT [28,30] and that access to treatment can be conditional on the results of the screening. It is clear that some form of qualification for treatment access other than age is needed once preventive treatment is available [38] in order to avoid overmedicating the whole population and unsustainable costs, but no answers are given as the topic is addressed only very sparsely in the literature. In this context, the question emerges whether it is ethical to restrict the access to DMT based on the results of model-based assessment of AD risk, given that for some proportion of patients they might be false [30]. Subsequent considerations, that the model could also biased, unreliable or otherwise faulty are not being discussed in the AD prevention literature. We elaborate more on these topics in discussion.

Instead, the main themes that emerge around the topic of treatment and conditioning of treatment access is equity and distributive justice, understood mostly as equal access of individuals at risk of AD to general health services as opposed to being discriminated against by insurers [22,28,55] and balance in the amount of stakeholders' attention and resources dedicated to preclinical AD, vs. dementia due to AD [12,24,30,36] vs. other healthcare needs [12,30,39,53,54]. In addition to that, the burden incurred to the healthcare systems by addressing preclinical AD is of concern [4,39,53].

Even once access to potential, future DMT is granted, an important uncertainty remains regarding the rationale for prolonged treatment in the preventive settings. There is a concern that possible side effects of preventive treatment [4,22,36], coupled with intensive and potentially invasive monitoring might in some cases overweigh the benefits [21,22,30,34,49,60]. Therefore future patients need to be informed about the benefits and risks of treatment to be able to weight these factors according to their own personal values and make an informed decision [28,59].

The concern regarding the benefit of future preventive treatment is amplified by uncertainty, as to whether a treatment benefit observed in clinical trials will represent the true effect in a real-world population of patients. This could happen if real-world patients are different, for example, more diverse than those recruited to the clinical trials based on stringent inclusion criteria [30]. A concern is raised also regarding whether the outcomes meaningful to patients will be adequately captured or at least informed by the clinical trials, which are typically limited in their time of follow-up [30,54]. This short time horizon of clinical trials is being seen as critical for the inability to make an accurate assessment of preventive treatment's real-world outcomes and cost-effectiveness [22,32,33,36,38,49,54,61]. Cost-effectiveness of both diagnostic tests and the preventive treatment is seen as a requirement for offering them to patients [55,61,62] but the literature diverges when it comes to opinions whether future AD treatment will be cost-effective or not. Some papers present claims that future early treatment will be superior to current symptomatic treatments, and that it will offset costs of healthcare and institutionalization. In such scenario, there is even an ethical obligation to make this treatment available to patients [22,40]. Opposite views dominate though due to a concern that the direct cost of innovative preventive treatment and of associated clinical monitoring will be large [22,30,31,36,38], while offsets will occur in the social care, rather than healthcare system [30,38]. Health-economic modeling can be used to resolve this dispute, however,

there is a caveat in that modeling is highly complex and the results depend on modeling assumptions. Therefore model inputs must be clearly defined and transparently communicated [38]. The literature does not provide answers yet as to what predictive power of a model used for preclinical testing would be desired and acceptable.

Broader social implications of using predictive models for AD prevention, and other social issues

The existing literature recognizes the need to facilitate development and adoption of effective AD strategies, given the major public health importance of AD. Public-private partnerships are often mentioned as an example of such strategies [12,30,31,33,36,61]. A sense of urgency can be seen regarding the need to regulate access to AD risk assessment which is already available to some patients through direct-to-consumer testing [40,56,58,61].

The future preventive approach to AD is expected to put a strain on the healthcare and social system, creating a demand for more intensive interaction between patient and doctor, assistance to people with preclinical AD to plan for and monitor emerging disabilities [22,31,63], and to provide care arrangements for them [31,38]. The existing literature recognizes the imminent tensions which might arise from this and calls for a priority setting process with public participation [28] and postulates that all patients in need have access to diagnosis and treatment, so as to prevent further health inequalities [22].

Further important ethical questions raised in the context of AD prevention using predictive modeling is how far medicine should go in terms of treating risk factors or risk status [12,31,56], and to what extent it should become “clinical-actuarial rather than clinical-pathologic” [31]. The rise of so-called “desktop medicine”, where patients learn about their health not based on their symptoms but test results introduce the need to appreciate

technological challenges, e.g. to develop an optimal governance model for patient's data, assure their privacy and accountability of those handling them [36,44]. Not to be ignored are also high technical and infrastructural requirements for data gathering and managing, particularly for population-level AD screening [22,30,36,38] and the need to adapt professional practices, social policies and legal infrastructure need to evolve to accommodate this paradigm shift in AD treatment [31].

Last but not least, it is worth noting that the topic of AD secondary prevention is discussed mostly from a perspective of high income countries, leaving out unanswered questions such as how these topics are being perceived outside the Global North [36,40] and whether low and middle-income countries possess means and infrastructure to also benefit from early AD diagnosis, management, and treatment [38]. The expectation is that the transnational gap will only increase once DMT become available [38].

DISCUSSION

This review investigated the ethical and social considerations which arise in the secondary AD prevention setting where predictive models can be used particularly for assessment of the risk of AD clinical symptoms in cognitively unimpaired individuals or prediction of long-term AD outcomes with and without treatment. The themes drawn from the reviewed literature reflect current academic discussion of those aspects that bear ethical or broader societal relevance, i.e. can be understood as statements regarding 'right' and 'wrong', the 'goodness' of practice or phenomenon, or competing normative interests and values among relevant stakeholders.

Much—although not all [38]—of the current literature is centered around the DMT being a necessary and sufficient condition for ethical risk assessment and disclosure. We did not identify articles discussing the benefit-to-risk of non-pharmacological interventions (e.g.,

cognition-based intervention, physical exercise) that may be effective in the early stages of AD [64], while better tolerated than pharmacological options. We argue that the discovery of DMT while resolving many critical issues related to AD prevention, creates others.

The first one is that the availability of a DMT will not automatically translate into accessibility, challenging the principle of equity and distributive justice. One can expect that such innovative treatment will be costly, at least during the first years after launch when it will be protected by a patent, and so will the battery of tests needed to select the target preclinical population. This means, that a large proportion of patients who could benefit from preventive treatment, insured in middle- and lower-income countries, might not have access to it and in high income countries paying for AD preventive treatment will off-set other healthcare or public needs..

The other issue introduced by the discovery of DMT is that despite overall efficacy demonstrated in a clinical trial, some aspects of drug's benefit-to-risk will remain unclear. This is because the long-term consequences of using this treatment will not be clear from the RCT alone, and because it will not be known whether all eligible patients will benefit from the treatment, and if not, whether some patients will be harmed. This issue, though, rooted in the ethical principle of non-maleficence, can be mitigated with further post-marketing studies, monitoring long-term consequences of such treatment and further scientific progress in the identification of potential responders, possibly leading one day to a stratified or even personalized medicine approach in AD. On the other hand, a rush in introducing a DMT into clinical practice in the preventive setting might severely limit our ability to adequately and comparatively monitor the long-term progression of AD and the long-term benefit to risk of any further treatments developed thereafter.

Finally, a side effect of the attempt to alter the AD trajectory and postpone, or even prevent cognitive decline and disability, is its contribution to creating a new patient population of "worried well" from individuals who otherwise considered themselves healthy, to the medicalization of private life, and to transforming medicine into an "actuarial" science and practice. These changes are not trivial. Positive AD risk assessment can impact self-perceptions or self-identity. Similar effects can occur for relatives, family members and friends who discover information about their susceptibility to AD, or learn about the susceptibility of a relative, resulting in (planned) modification of familial, social, or caring roles. AD risk assessment may likewise result in discrimination comparable to that facing symptomatic AD dementia patients, family members, and carers. People at risk of AD (i.e. who may or may not develop AD dementia at some point in the future) may, for example, also be exposed to attitudes, practices or procedures which potentially devalue or discriminate against them (e.g. monitoring their ability to manage finances or to drive already before the symptoms occur, perhaps even as a part of a well-intended policy). This is while patients often fear loss of agency more than they fear death [43], perhaps because of the social stigma associated with AD, overemphasizing the most advanced stages of AD, as opposed to providing support allowing people affected by AD to function in various domains in life as long as possible.

Another finding from this review is that although ethical issues in AD secondary prevention are discussed abundantly in the literature, specific issues related to modeling used to predict AD risk are not scrutinized. One instance of this is the existing literature around disclosure practices which seems to be deeply anchored in the paradigm of a single risk factor, primarily genetic, or to a lesser extent, biomarker-related. Assessment of personal risk estimated using advanced predictive methods, combining a number of patient characteristics as described above (e.g. demographics, genetics, brain images, blood biomarkers, and medical history) is

scarce and incomplete. For example, the uncertainty around the prediction of AD is typically understood in the literature as the probability of making a false-positive diagnosis and therefore raises the problem of misclassification by a predictive algorithm. The reviewed literature is likewise missing any specific considerations regarding the clinically and socially acceptable levels of precision and reliability of the models which could be used in the AD secondary preventive setting and therefore, it is currently not possible to derive from the literature any indication about the qualities of a predictive algorithm that would justify its use in populations known to be at risk, and in the general population.

Also specific sources of uncertainty and biases leading to misclassification are not being discussed. Such biases can be purely technical (e.g. low granularity of data for prediction affecting the precision of prediction) but can also be rooted in social attitudes and practices, either pre-existing at the time when a predictive model is being developed or emerging during and through the use of this model [65]. As a hypothetical example, a person whose relative have AD might be more likely referred to a specialized memory clinic compared to a person without this risk factor (preexisting bias) resulting in data from memory clinics overrepresenting this type of future patients (technical bias). In effect, a model developed on such data could produce more accurate predictions for this group of patients, compared to others (external generalizability). Such a model subsequently used in a clinical practice could then contribute to the underrepresented patients receiving suboptimal care or even to being discriminated against. The clinical use of such a complex, multivariate predictive model would pose more challenges. For example, the same level of risk can be derived from such a model for two patients based on completely different sets of characteristics, and therefore, be associated with a different degree of uncertainty. This feature might make the AD prediction based on such a model more demanding to communicate to both the patient and the treating physician. If machine learning was used to develop the model, which is increasingly the case,

it would even be very difficult to trace back the reasons why a certain prediction was made. In additional to that, commercially developed models will likely be patented and not open for public scrutiny. Therefore, any potential harm caused by biased prediction would be difficult to discover, posing a risk that a faulty model would shape the clinical practice for an extended period of time and leading to a dispute who is to be held accountable for the fault of a self-learning predictive model [66]. In this new context data governance needs to be reassessed, starting from fundamental issues such as informed consent (To what extent is it possible, given the complexity and unknown long-term consequences of using predictive models in routine care?) and data privacy (How to assure that patients will not be de-identified based on a unique set of characteristics used in the multivariate predictive model?), through ownership (If patients or clinics contributed data to develop a model, who owns the model?) and accountability (What business model would best strike balance between model developers rights and profits and public interest?), all the way to very specific consideration around data sharing for modeling purposes. The latter is a challenge because unlike in the case of descriptive analytics which can be generated internally within the institution of a data owner and shared externally, building a predictive model requires multiple iteration of access to data which can hardly be done without a physical access.

Furthermore, the existing literature on Alzheimer's Disease barely mentions a possibility that a predictive model can serve not only as an elective preventive procedure, but also as a basis for a populational surveillance system, e.g. when connected to an Electronic Medical Record (EMR) system, and this is despite the growing interest in using EMR for public health surveillance and case detection [67,68]. In AD setting, patients identified by one predictive algorithm with high sensitivity and low specificity could be called into a healthcare practice for an AD risk assessment, using a more specific algorithm, e.g. including biomarkers. Sparsely covered is the problematic of the large technical and infrastructural requirements of

AD secondary prevention. Any extensive use of such advanced models predicting risk of future AD will have large logistic requirements for data collection, processing and storage.

While these large themes are clearly underrepresented in the current literature on AD, a discussion around mathematical models used to predict future AD outcomes for the needs of health technology assessment is emerging. The most straightforward example of such a model is a health-economic model which will be needed to evaluate the cost-effectiveness of the preventive AD treatments, once they are developed. It is being recognized that results of such a model will depend to a large extent on the choice of the modelled outcomes and assumptions. Therefore, established criteria for such model's trustworthiness are needed, so that it could be used for decision making. As part of this effort, a series of studies have been conducted in the ROADMAP project (Real World Outcomes across the AD Spectrum for Better Care) [69], focusing on the ethical and social implications of data sharing and repurposing, priority outcomes for different AD stakeholders and methodologies as well as input data used in the currently existing health-economic models in AD [70,71]. Reporting standards have also emerged for both economic evaluations and predictive models (CHEERS and TRIPOD, respectively) [72,73].

FUTURE DIRECTIONS

This review uncovered several directions for future research.

The first one would be to supplement the current review conducted in the AD setting, with a review of literature on the developments in the field of predictive modeling, machine learning, and precision medicine, which—even if not specific to AD—could provide a perspective on specific challenges to be expected if predictive models are used in routine clinical care. Some lessons can also be learned from other specific fields were predictive modeling was applied to assess credit score, predict child abuse, criminal offence, among

others [74]. Such a review could also further explore how the use of predictive models for preclinical risk assessment can affect access to preventive treatment. For example, whether risk stratification could lead to unfair exclusion of people who might desire to receive a preventive AD therapy, but be denied access, if not meeting a certain pre-defined risk threshold.

The second direction would be to examine the perspectives on secondary AD prevention from low- and middle-income countries, given that the reviewed literature discussed mostly the high-income countries perspective. Some of the differences which we expect to see would be in beliefs about the benefits of risk disclosure and in considerations and realities of limited access to current and future AD therapies.

Finally, another topic to explore is the possible policy consequences of a large scale AD prevention. The literature suggests that focus on prevention would divert resources from care offered to symptomatic AD patients. It is, however, possible that standards of AD care improve, if large scale AD risk assessment creates an organized group of cognitively unimpaired people aware of their likely future with AD clinical symptoms and ready to engage in policy making.

LIMITATIONS

One potential limitation of this study is that it reflects the current status of the ethical discussion about the ethical aspects of using predictive modeling in AD secondary prevention. We found that this discussion does not yet follow the most recent medical developments in the AD field. Similarly, we did not identify articles discussing the benefit-to-risk of non-pharmacological interventions (e.g., cognition-based intervention, physical exercise) that may be effective in the early stages of AD, while better tolerated than pharmacological options [64].

Another potential limitation stems from the fact that the mapping of ethical themes relies to a large extent on qualitative interpretation of the reviewers. To mitigate the risk of self-nomination eight principles were used as guidelines to establish the ethical relevance of each theme. The eight principles are not intended as an ethical framework for predictive modeling, but rather were used as a reference point to further establish the ethical relevance of the themes identified in the reviewed studies beyond self-nomination by study authors.

CONCLUSIONS

Based on our understanding of the AD and therapeutic landscape in this indication, we believe that advanced predictive modeling might become an indispensable element of AD preclinical prevention. In such scenario, given the numerous ethical concerns associated with this approach, safeguards need to be implemented. Public health and medical institutions undertaking AD preventive programs are accountable to the general public and patient populations whose health and well-being are at stake. Risk-benefit assessments, model validation, and development of professional practices and norms are necessary to establish and deliver effective and publicly beneficial screening programs and treatment access plans. Evidence supporting the implementation of such programs should be shared with relevant patient populations to support well-informed autonomous decision-making regarding participation.

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Contributors

ZA, CN, HK drafted the protocol. ZA supervised all aspects of the study including document screening, selection, reconciliations, data extraction and management, analysis, and reporting. MN developed search terms. ZA, CN, HK, AT, DG, JS and AK screened the abstracts, reviewed the manuscripts, extracted and analyzed the content. BM conducted the analysis of the ethical principles embedded in the themes. ZA, CN, AT, DG, HK, AK, JS, BM and FdRdV made substantial contributions to conception or design of the work and reviewed the manuscript for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The

ROADMAP consortium reviewed this protocol before submission to the journal. ZA is the guarantor of this review.

Competing interests

This SLR is being conducted as part of the ROADMAP project. ROADMAP is a consortium of academic, public sector and industry partners working collaboratively within the European Union Innovative Medicines Initiative framework. ZA, HK, CN, JS and MN are employees of Analytica Laser, a Certara company which received consulting fees from Novartis and other pharmaceutical companies. DG is an employee of Alzheimer Europe. FdRdV is employee of Novartis Pharma AG. AK is employee of Janssen Pharmaceutica NV.

Ethics

This study did not involve human or animal experimentation.

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Tables

Table 1 Criteria for study selection with instructions for reviewers and examples

	Included	**Excluded**
Setting	Documents discussing pre-symptomatic/ asymptomatic individuals at-risk of AD, including those with subjective memory complaint/cognitive impairment but without MCI diagnosis. Examples: asymptomatic patients with genetic predisposition, family history, presence of AD biomarkers, abnormal biomarkers, treatment prior to onset, cognitively intact, cognitively normal, prodromal AD (*only if understood as asymptomatic, when in doubt or not specified/clear --->include*),	Documents discussing ONLY symptomatic stages of AD; documents discussing dementia secondary to other diseases as well as other primary dementias. Examples: MCI (Mild cognitive impairment) or prodromal AD (*if defined as encompassing first symptoms*); cardiovascular dementia, alcohol/drug, metabolic/diabetic/insulin resistance, Lewy body dementia
Intervention	Documents discussing either the predictive modeling method (statistical algorithms) or source data (including secondary data re-use) as a component of secondary AD prevention. *Secondary prevention is - targeting asymptomatic/pre-symptomatic people at-risk of AD, preventing disease or delaying its onset.* Example of potential data sources for predictive modeling: Genetic - Presenilins (PSEN-1, PSEN-2), APOE4; Imaging - PET scan, MRI; Cerebrospinal fluid (CSF); Electronic/Medical Health Record; Biomarker status (Amyloidosis, Amyloid-β, Aβ, tau); Comorbidities; Family history of AD	Documents discussing secondary prevention but without any component of predictive modeling (neither method, nor data source); documents which do not discuss secondary prevention of AD (e.g. discuss tertiary prevention targeting individuals with MCI and later). *Tertiary prevention is slowing down the progression once symptoms/MCI or AD dementia occurs.*
Evaluation	Ethical discussion or commentary on secondary prevention of AD supported by predictive modeling (as indicated in the abstract) is present.	Ethical discussion or commentary on secondary prevention of AD supported by predictive modeling (as indicated in the abstract) is absent.
Publication date	2007-2018	All prior to 2007
Language	Full text in English, French or German	Full text in any other language

Study type	Primary and secondary research on humans (clinical, social, observational, RCTs, reviews, meta-analyses), abstracts, posters, editorials, commentaries, discussion and position papers and other media, conference abstracts, books and book chapters, reports	Animal studies, In-vitro studies, Study protocols,

Table 2. Results of individual studies

Theme/Sub-theme	Ethical concern (EC) or Social Implication (SI)?	References*
Selection of a population for risk assessment via predictive modeling		
1. AD risk assessment is not ethical without sound treatment options, therefore existence of a disease-modifying treatment is a pre-requisite for population AD screening.	EC	[21,22,46–54,24,28,32,33,35,37,40,43]
2. Patients participating in screening might be misdiagnosed, given that adequate diagnostic tests for preclinical AD are currently not available. False positive diagnosis is of particular ethical concern.	EC	[21,30,33,42,43,54]
3. There is no social consensus regarding the sufficient predictive value of a set of tests, or other test's characteristics, that would give social legitimization to population screening.	SI	[21,38]
4. AD risk assessment will lead to over-diagnosis and potential harm…	EC	[4,12,33,37,40–42,54,21,23,24,28–32]
a. …because of the slow disease progression/competing risks.		[36,54]
b. …because of unknown validity of biomarkers in the clinical practice (e.g. lack of evidence that Aβ plaques are causal for the disease).		[37,40,42]
c. …because diagnostic tests can have side effects.		[30,41]
5. Population screening for preclinical AD will transform healthy individuals into preclinical AD patients.	SI	[12,21,23,24,28–33]
6. It is not ethical to withhold a possibility to undergo AD risk assessment from people who are interested in learning about their genetic and overall risk level.	EC	[34]
7. Access to AD risk assessment should be limited to people with good predisposition to handle it ("Screening before screening") to mitigate its adverse consequences.	EC	[12,21,28,31,35–37]
8. Certain safeguards are needed before offering access to AD risk assessment, such as…		[28,31,35,39–45]
a. …provision of appropriate information and education.	EC	[28,31,35,39–44]
b. …receipt of informed consent.	EC	[28,31]
c. ….assessment of impact of the AD risk assessment on individual and/or family level (need for individualization of the clinical practice).	EC	[39,40]
d. …defining a standardized process, incl. developing diagnostic/predictive modeling guidelines (need for standardization of the clinical practice).	EC, SI	[31,35,39,41,45]
e. …adaptation of professional practices, definition of social policies and laws to prevent stigmatization of individuals at risk of AD.	EC, SI	[31,39,40,42–44]
Disclosure of individual risk assessed using predictive modeling		
9. Certain pre-requisites are needed for ethical disclosure of individual AD risk, such as…		[4,31,35,39,40,58,59]
a. …establishing that the risk assessment provides meaningful clinical information (otherwise there is no obligation of disclosure).	EC	[4,31]

	b. …being able to offer a disease-modifying treatment to patient (in which case arises an obligation to disclose the risk).	EC	[58]
	c. …receiving an explicit request from the patients, since patient's autonomy is decisive for whether a disclosure should be made or not. Further on, patient's willingness to know might mediate the benefit from the AD risk assessment.	EC	[4,35,40,58]
	d. …establishing a positive individual benefit-risk, taking into account patient/carer characteristics, family sphere and external environment.	EC, SI	[39,40,59]
10. Disclosure of risk status brings about positive consequences for the individual undergoing assessment, such as…			[4,12,48,53,55–58,30–32,35,37,39,40,43]
	a. …potential alleviation of anxiety associated with uncertainty of their AD risk.	EC	[37,39,53]
	b. …creating a possibility for future planning (will, power of attorney, future changes, lifestyle changes, pre-emptive suicide).	EC	[4,12,55–58,30–32,35,37,40,43,48]
11. Disclosure of risk status brings about negative consequences for the individual undergoing assessment, such as…			[4,12,40,43–45,49,53,55–58,21,22,28,30,36–39]
	a. …potential induction of anxiety associated with living for years without a certainty of diagnosis, until symptoms occur.	EC	[12,30,36,37,40,53]
	b. …potential false-positive diagnosis, causing people to live for years with a threat of a non-existent disease.	EC	[38,53]
	c. …potential overburdening and overmedicating of people with high AD risk.	EC	[30,58]
	d. …potential employment/workplace discrimination and social stigma.	EC	[21,22,58,28,39,40,44,45,49,55,57]
	e. …potential depression, distress or suicidal attempts among individuals with a high AD risk.	EC	[4,37,40,43,49,56]
	f. ...potential objective limitation of people's performance due to stereotyping based on a high AD risk.	EC, SI	[12,30]
12. Disclosure of risk status brings about negative consequences for the family of individuals undergoing screening, such as…			[39,40,53]
	a. …anxiety and uncertainty among relatives and significant others, who empathize with the individual with high AD risk or who might be overburdened with care responsibilities.	EC	[39,40]
	b. …anxiety among the relatives, who become aware of their own individual risk (risk of familial AD).	EC	[40,53]
13. There is a risk of miscommunication and therefore misinformation while disclosing the risk status to individuals, given the complexity of the issue and the associated uncertainty, which is further complicated by…		EC	[12,28,38,39,53,58]
	a. …patients' heterogeneous characteristics and predispositions.		[28,39,53]
	b. …characteristics of the specific method or test used to assess the risk status.		[38,58]
Treatment and preconditioning of treatment access based on predictive modeling			
14. Preventive AD treatment raises concerns from the perspective distributive justice, such as…		EC	[12,24,30,36,39,53,54,63]

	a. …diverting resources from current symptomatic AD patients.	EC	[12,24,30,36]
	b. …diverting resources from other health needs which might be more immediate than future Alzheimer's dementia.	EC	[12,30,54]
	c. …potential weakening of the health system, due to the fact that insurers will not be able to act upon client's AD risk status or will not be at all informed about the elevated risk in their clients (in certain health-care settings).	SI	[39,53]
15. Early treatment for preclinical AD raises concerns from the perspective of equity, such as…		EC	[22,30,38]
	a. …concern that it is not ethical to restrict access to treatment based on age (assuming a scenario, in which people above some threshold of age are preventively treated for AD).	EC	[38]
	b. …concern that it is not ethical to restrict treatment access based on risk assessment, because it might be false (assuming a scenario, in which only people with high risk are preventively treated for AD).	EC	[30]
16. People with high risk of AD might face restriction in access to non-AD related health care services (e.g. transplant, health insurance).		EC	[22,28,55]
17. Both preventive treatment and diagnostic tests needs to demonstrate cost-effectiveness, before they can be offered to patients.		EC, SI	[55,61,62]
18. In absence of DMT, the value of an AD risk assessment is limited, as it merely extends the time spent as a patient, awaiting treatment or symptoms.		EC	[28,30]
Assessment of the benefit from treatment based on predictive modeling			
19. The clinical rationale of prolonged preventive treatment has limitations, due to…			[4,21,60,22,30,33,34,42,48,49,54]
	a. ...possibility of adverse events due to treatment, which might overweigh the benefit.	EC	[4,22,36]
	b. …potentially large impact of the cost of preventive treatment on payer's/insurer's budget.	SI	[4]
	c. …adverse consequences of repeated monitoring of disease progression, and repeated testing, which might be invasive, time consuming and expensive.	EC	[21,22,30,34,48,49,60]
20. Decision to undergo preventive treatment should be based on individual's personal benefit-to-risk assessment, according to their personal values, but adequate knowledge information about treatment might not be available.		EC	[28,59]
21. There is uncertainty as to whether treatment benefit observed in clinical trials will translate to the real world setting of usual care, because…		EC	[30,54]
	a. …there is no consensus around the endpoints/outcomes relevant in real world setting, and about their sensitivity.		[30,54]
	b. …time of follow-up in clinical trials is insufficient to make conclusions about treatment outcomes that would be meaningful to patients.		[30]
	c. …there are inherent differences between patient populations typically enrolled in the clinical trial and real world patients.		[30]
22. The possibility to make an accurate benefit-to-risk assessment is hampered by other unknown factors, such as…			
	a. …unknown time horizon until the exact consequences of preventive AD treatment are known, in regard of both real world effectiveness and cost-effectiveness.	EC	[22,32,33,36,38,49,54,61]

23. There is an ethical obligation to offer preventive treatment on the grounds of its superior cost-effectiveness, comparing to symptomatic AD treatments. Claims of superior cost-effectiveness are based upon assumptions that…	EC	[22,40]
a. …there will be a large offset of societal burden due to avoiding/delaying institutionalization once preventive treatment is used.	SI	[22]
b. …there will be a significant offset of overall health costs once preventive treatment is used.	SI	[40]
24. There are concerns about whether the preventive treatment, once available, will be cost-effective, because	SI	[22,30,31,36,38,40]
a. …costs of innovative, disease-modifying preventive treatment will be substantially higher than the cost of symptomatic treatment. Huge budget impact of preventive treatment is expected.	SI	[38]
b. …offset of societal burden will occur in a different sector that the one which pays for treatment.	SI	[30,38]
c. …the societal burden associated with AD prevention (e.g. specialists visits, imaging) will be large.	SI	[22,30,31,36,38]
25. When modeling is used to alleviate challenges in value assessment, there is a caveat in that modeling is highly complex and the results depend on modeling assumptions. Therefore, modeling might also be misguiding.	EC	[38]
26. Trustworthiness of predictive and health-economic models increases when input data to the model are clearly defined.	EC	[38]
Broader social implications of using predictive models for AD prevention, and other social issues		
27. Broader implications for medicine and health-care include…		[12,22,31,38,56,63]
a. …increasing relevance of "desktop medicine", with patients learning about their medical condition not based on their symptoms, but based on test results. This poses a question, how far to extend treatment of risk factors.	SI	[12,31,56]
b. …increasing relevance of risk-based, clinical-actuarial rather than clinical-pathologic medicine.	SI	[31]
c. …creating a demand for more intensive interaction between patient and doctor and for assistance for people with high risk of AD to plan for and monitor emerging disabilities.	SI	[22,31,63]
d. …creating a demand for new, multisectoral care arrangement for people with high risk of AD.	SI	[31,38]
28. Broader implication for society include…		
a. …the need to facilitate development and adoption of effective AD strategies, given the major public health importance of AD and increasing unmet need. These strategies can include public-private partnerships.	SI	[12,30,31,33,36,61]
b. …the need to facilitate or regulate access to AD risk assessment, given that such practices are already present (clinical practice precedes the policy).	SI	[40,56,58,61]
c. …the need for priority setting process to address distributive justice issues and public engagement into shaping the science.	SI	[22,28]
29. An appreciation of cultural differences which might influence attitudes towards AD risk assessment is needed.	SI	[36,40]

30. An appreciation of the transnational gap in access to diagnosis and treatment is needed. This gap is expected to increase once disease-modifying treatment is developed.		SI	[38]
31. An appreciation of technological challenges is needed. Such challenges might include:			
	a. …the need to ensure privacy of patient's data and accountability of those handling them and potential disputes over optimal governance model.	SI	[36,44]
	b. …potential disputes over optimal governance model.	SI	[36]
	c. …high technological and infrastructural requirements for data gathering and managing, particularly for population-level AD screening.	SI	[22,30,36,38]

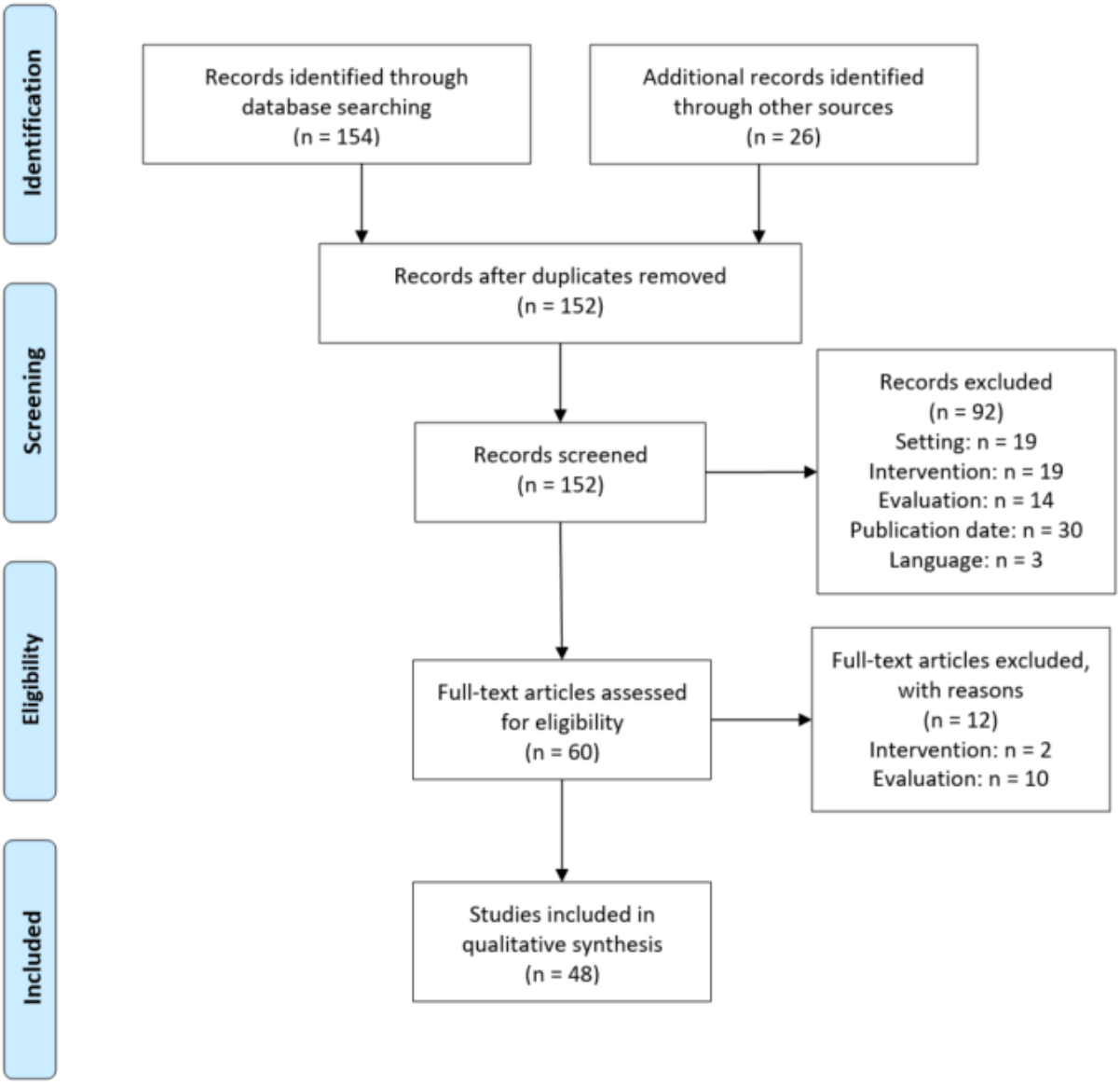
** References are nested, meaning that a reference for a sub-theme populates the reference to the main theme whenever appropriate.*

Table 3. Mapping of ethical themes to underlying ethical principles

Ethical principle	*Definition*	*Relevant ethical themes*
Respect for autonomy	Individuals must be treated as autonomous agents capable of deciding whether to participate in a proposed intervention.	6, 8a, 8b, 9c, 10a, 10b, 20, 27a
Beneficence	Medical interventions should maximize possible benefits to the affected population.	1, 8a, 9a, 9b, 9d, 10a, 10b, 14b, 18, 21b, 21c, 23a, 24a, 24c, 28a
Non-maleficence	Medical interventions should minimize possible harms to the affected population.	2, 4a, 4b, 4c, 7, 11a, 11b, 11c, 11e, 12a, 12b, 16, 19a, 19b, 19c, 22a, 25
Equality, justice and diversity	The risks and benefits of a proposed intervention should be fairly distributed across affected stakeholders.	3, 5, 8c, 11c, 11d, 14a, 14b, 14c, 15a, 15b, 16, 17, 19d, 19f, 23a, 23b, 24a, 24b, 24c, 27c, 27d, 28a, 28b, 28c, 29, 30
Identity and stigma	Patients should not be exposed to the risk of being discredited and discriminated against.	5, 8c, 8e, 11b, 11c, 11d, 11f, 12b, 18, 27a, 27c
Privacy	Information entrusted by patients should be safeguarded from inappropriate use.	8c, 12b, 31a, 31b, 31c
Accountability, transparency and professionalism	Medical professionals and decision makers have moral obligations and duties to patients and the public, based on broader ethical and moral codes, standards, and traditions.	8, 8d, 8e, 9a, 9b, 13b, 21a, 25, 26, 27a, 27b, 27d, 28c, 30, 31a, 31b
Uncertainty avoidance	The need for patients to take decisions with unpredictable outcomes should be minimized.	1, 9a, 10a, 10b, 11a, 12a, 13a, 13b, 15b, 21a, 21b, 21c, 22a

Figures

Figure 1 PRISMA flow diagram



Supplementary file 1: PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 checklist

Source: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339(jul21 1):b2535-b2535. doi:10.1136/bmj.b2535

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. → Yes, in title	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). → see section: Objectives and Table 1	7, 48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. → see section: Protocol development	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. → see section: Study selection	9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. → see section: Search methods and Supplementary file 2	9, 54
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. → see Supplementary file 2	54

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). → see sections: Study selection and Data collection and extraction	9, 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. → see section: Data collection and extraction	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. → see section: Data collection and extraction.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. → see section: Risk of bias	11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). → Not applicable	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. → see section: Data analysis	10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). → see section: Risk of bias	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. → Not applicable	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. → Yes, provided	49
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. → see section 'Study selection', 'Data collection and extraction' and 'Study characteristics' where we present we present study characteristics. More details on the type of extracted data are included in the study protocol[19].	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). → Not applicable, see section: Risk of bias (quality assessment)	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. → Not applicable	
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency in accordance with the text in the Explanation and Elaboration document. → see section: Results of the individual studies.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15). → Not applicable, see section: Risk of bias	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). → Not applicable	

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19 onwards
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25, 27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. → see sections: Funding, Acknowledgements, Contributors and Competing interests	28

Supplementary file 2: Full electronic search strategy and the retrieved results

Data source	Search terms	Element of the framework
Embase/Medline® Daily, Epub Ahead of Print, In-Process & Other Non-Indexed Citation Date of search: 2018-05-28	(Alzheimer$.ti,ab,kw. or Alzheimer Disease/) and (asymptomatic disease?/ or (preclinical or pre-clinical or presymptomatic or pre-symptomatic or asymptomatic or (amyloid$ adj2 positiv$) or atrisk or at risk or (biomarker adj positive) or biomarker based or cognitively normal or cognitively intact or early stage or early phase).ti,ab,kw.)	25913
	(prediction or (predict$ adj2 (model$ or analytic$)) or prevention or early intervention$ or early treatment$ or early diagnos#s or early detection).ti,ab,kw. or prediction/ or secondary prevention/ or early diagnosis/ or early intervention.sh.	2215809
	(ethic$ or ELSI or (social adj3 (issue$ or aspect$ or impact$ or consequence$ or implication$ or effect$ or consideration$ or challenge$))).ti,ab,kw. or ethics/ or medical ethics/ or exp research ethics/ or exp bioethics/ or Bioethical Issues/ or professional ethics/ or clinical ethics/ or ethics.fs. or Ethical Analysis.sh. or **Ethical Review/** or Principle-Based Ethics.sh. or social aspect/	573274
	Setting **AND** Intervention **AND** Evaluation	Final search (112 after automatic deduplication)
PsycInfo Date of search: 2018-05-31	(Alzheimer$.ti,ab. or Alzheimer Disease/) and (asymptomatic disease?/ or (preclinical or pre-clinical or presymptomatic or pre-symptomatic or asymptomatic or (amyloid$ adj2 positiv$) or atrisk or at risk or (biomarker adj positive) or biomarker based or cognitively normal or cognitively intact or early stage or early phase).ti,ab.)	5338
	(prediction or (predict$ adj2 (model$ or analytic$)) or prevention or early intervention$ or early treatment$ or early diagnos#s or early detection).ti,ab. or prediction/ or secondary prevention/ or early diagnosis/ or early intervention.sh.	189810
	(ethic$ or ELSI or (social adj3 (issue$ or aspect$ or impact$ or consequence$ or implication$ or effect$ or consideration$ or challenge$))).ti,ab. or ethics/ or medical ethics/ or exp research ethics/ or exp bioethics/ or Bioethical Issues/ or professional ethics/ or clinical ethics/ or Ethical Analysis.sh. or Ethical Review/ or Principle-Based Ethics.sh. or social aspect/	130712

	Setting **AND** Intervention **AND** Evaluation	Final search (19 after automatic deduplication from MEDLINE)
SCOPUS Date of search: 2018-05-31	(TITLE-ABS-KEY (Alzheimer* AND (pre-clinical OR pre-symptomatic OR asymptomatic OR "amyloid* positive" OR at-risk OR "biomarker positive" OR "cognitively normal" OR "cognitively intact" OR “biomarker based” OR “early stage” OR “early phase”)))	10262
	(TITLE-ABS-KEY (prediction OR “predict* model*” OR “predict* analytic*” OR prevention OR “early intervention” OR “early treatment” OR “early diagnosis” OR “early detection”))	2706873
	(TITLE-ABS-KEY ("ethic*" OR "ELSI" OR "social issue*" OR "social aspect*" OR “social impact*” OR “social consequence*” OR “social implication*” OR “social consideration*” OR “social challenge*”))	495027
	Setting **AND** Intervention **AND** Evaluation	Final search 23 (after deduplication from MEDLINE)
Google generic search engine part1 (“Ethics”) Date of search: 2018-04-25	Alzheimer AND (preclinical OR pre-symptomatic) AND (prediction OR prevention OR (early intervention) AND (ethic OR ethical) AND (issue OR problem OR concern OR implication)	248 000, first 10 webpages with results screened (13 retrieved)

Google generic search engine part 2 (“Social implications”) Date of search: 2018-07-12	Alzheimer AND (preclinical OR pre-symptomatic) AND (prediction OR prevention OR (early intervention) AND ((societal implication) OR (societal issue) OR (societal problem) OR (societal concern))	109 000, first 10 webpages with results screened (9 retrieved)
Targeted websites via Google search interface* Date of search: 2018-07-30	As for Google generic search engine	4 retrieved

* Alzheimer Europe (https://www.alzheimer-europe.org/), Alzheimer’s Association (https://www.alz.org/), Alzheimer’s Foundation of America (https://alzfdn.org/); Alzheimer’s Society, UK (https://www.alzheimers.org.uk/); France Alzheimer (https://www.francealzheimer.org/); The World Health Organization (http://www.who.int/), The Organization for Economic Co-operation and Development (http://www.oecd.org/).)

Supplementary file 3: Alphabetic list of reviewed publications

Albert MS, Mckhann GM (2011) *Neuroethical Issues In Early Detection Of Alzheimer'S Disease*, Oxford University Press.

Alzheimer_Europe (2011) Ethics of dementia research. Chapter 9: Dementia Research.

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Illes J, Rosen A, Greicius M, Racine E (2007) Prospects for prediction: Ethics analysis of neuroimaging in Alzheimer's disease. *Ann. N. Y. Acad. Sci.* **1097**, 278–295.

Johnson RA, Karlawish J (2015) A review of ethical issues in dementia. *Int. Psychogeriatrics* **27**, 1635–1647.

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