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

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ABSTRACT

Introduction The therapeutic paradigm in Alzheimer's disease (AD) has shifted towards secondary prevention, defined as an intervention aiming to prevent or delay disease onset in pre-symptomatic individuals at risk of developing dementia due to AD. The key feature of AD prevention is the need to treat years or even decades before the onset of cognitive, behavioural or functional decline. Prediction of AD risk and evaluation of long-term treatment outcomes in this setting requires predictive modelling and is associated with ethical concerns and social implications. The objective of this review is to identify and elucidate them, as presented in the literature.

Methods and analysis A systematic literature review was conducted in Medline, Embase, PsycInfo and Scopus, and was complemented with a grey literature search. All searches were conducted between March and July 2018. Two reviewers independently assessed each study for inclusion and disagreements were adjudicated by a third reviewer. Data are now being extracted using an extraction sheet developed within the group of reviewers, based on an initial sample of three manuscripts, but allowing for inclusion of newly identified data items (ethical arguments). Data will be analysed qualitatively using a thematic analysis technique. Potential biases in selection and interpretation of extracted data are mitigated by the fact that reviewers come from a range of different scientific backgrounds and represent different types of stakeholders in this ethical discussion (academia, industry, patient advocacy groups).

Ethics and dissemination The study does not require ethical approval. The findings of the review will be disseminated in a peer-reviewed journal and presented at conferences. They will also be reported through the Innovative Medicine Initiative project: Real World Outcomes Across the AD Spectrum for Better Care: Multi-modal Data Access Platform (IMI: ROADMAP).

Trial registration number CRD42018092205.

Strengths and limitations of this study

► This is the first systematic literature review of the ethical concerns and social implications which arise due to recent scientific and technological progress which enables AD prevention at asymptomatic stages.

► Detailed and robust methodology was developed to ensure producing a possibly valid and complete ethical and social landscape of AD secondary prevention using predictive modelling.

► Potential limitation of the study is that the current literature might not be sufficiently mature to capture all relevant ethical concerns and social implications.

INTRODUCTION

Alzheimer's disease (AD) is the cause of 70% of all dementias[1] and a significant public health challenge both in the developed and the developing countries. Dementia due to AD is clinically characterised by cognitive and executive dysfunction, psychiatric symptoms and behavioural disturbances. It leads to difficulties performing activities of daily living and eventually to death.[2 3]

Until recently, AD could be assumed from a relatively early age of patients at onset and clinical observation, yet the final diagnosis could only be made postmortem based on a brain autopsy.[4] Treatment strategies for patients with assumed AD became available only at the end of the 20th century, through marketing authorisation for cholinesterase inhibitors indicated for mild to severe AD dementia. Shortly thereafter, N-methyl-D-aspartate *antagonist* memantine was authorised for use in moderate to severe AD dementia. These treatments help manage dementia symptoms but do not alter substantially the disease course.[5] The 21st century has seen a tremendous progress in the field of AD biomarkers discovery. Measuring these biomarkers, such as the presence of amyloid βeta (Aβ) plaques in brain or in the cerebrospinal fluid, is nowadays a routine practice in

AD research and is slowly entering the clinical setting as well.[6] Thanks to biomarker discovery, it became possible to more precisely distinguish between dementia due to AD versus other types. More importantly though, it became possible to identify potential AD patients in a preclinical stage which is characterised by elevated levels of AD biomarkers yet in the absence of clinical symptoms.[7–9] This opens a new and potentially the only avenue for disease modifying AD treatment, particularly since of all phase three trials targeting symptomatic AD failed.[10] It is now believed that the same drugs which were not efficacious in AD dementia might turn out disease modifying if used early enough.[11]

Recognition of a continuous character of AD, progress made towards identification of AD-like pathology in cognitively intact people and increasing belief that only early treatment can be disease modifying caused a major shift in the therapeutic paradigm in AD. This shift has been from dementia symptoms management to secondary prevention, understood as intervention in presymptomatic 'at-risk' individuals to prevent or delay disease onset.

Together with the technological progress made in the recent decades with regard to availability of patient's data, diminishing cost of data storage and computing power, these developments make it now feasible to assess the risk of developing AD in large number of potential patients and implement preventive approaches in clinical practice or a public health measure.

Yet preventive approach in preclinical AD brings about numerous ethical concerns and social implications which, even if not specific to AD, require a close investigation in this particular setting. What makes the case of AD distinct is apparent need to intervene years (or even decades) before the onset of cognitive, behavioural or functional declines which impact patients' lives,[12] without having a sufficient understanding of causal mechanisms of the disease to assess long-term consequences of this intervention. In this setting where link between cause, intervention and the effect is uncertain and spread over a long period of time, the use of predictive modelling is particularly needed. Specific challenges of AD prevention and how predictive modelling can help address them, is summarised in table 1.

Predictive modelling can however act as double-edged sword and while facilitating some challenges arising in the context of AD prevention, it also adds numerous ethical concerns and social considerations potentially stemming from—among others—the risk of false classification, the dependence of the results on the assumptions, and from the statistical complexity which makes it difficult to communicate the modelling concept and results to general public, and to an individual patient.

Table 1 Principles of secondary preventive approach as applied to Alzheimer's disease (AD) and the role of predictive modelling in this setting

Criteria	Prerequisites for a preventive approach	AD-specific context	Role of predictive modelling
Importance and public consensus	Large unmet public health causing a public concern.	Yes: there is a public consensus around the unmet need and its criticality. Further to that, prevention might be the only feasible intervention in AD (speculative).	–
Costs	Prevention is more cost effective than treatment over the lifetime of the patient.	Likely the case, given the AD burden, but not conclusive (until a specific intervention is evaluated).	Health-economic modelling with a long-term horizon depending on long-term scenario.
Mechanism	The natural course of disease is well understood.	The role of a myloid βeta (targeted by the currently developed drugs) for disease progression is only partially understood, therefore reducing its levels might not translate to improvement in clinical outcomes.	–
Selection of the population to receive intervention	Intervention is offered to all demographic segments in the population or specific screening procedure exists.	Population-wide treatment might not be appropriate (side effects, budget impact). Targeting a segment might be necessary but difficult to establish which one (only a partial match between the asymptomatic stage and AD, genetic markers not conclusive).	Identification of 'at-risk' patients from a general population or a predefined population with individual factors (eg, with genetic predisposition, family history, subjective memory complaint, etc.)
Efficacy of the treatment	A disease-modifying treatment exists.	Future phase three trials will conclude on some but not all meaningful outcomes.	Prediction of clinical outcomes and long-term based on biomarker status and its trajectory (eg, cognition vs function and dependency).
Access to treatment	Efficacious treatment is accessible and affordable.	Not possible to conclude until a specific intervention is known.	Identification of patient subgroups most likely to benefit from the treatment.

Source, criteria and prerequisites adapted from Khoury et al[36] and Wilson and Jungner[13]

The objective of this study is to systematically review and discuss the ethical concerns and social implications raised by the use of predictive modelling tools in the setting of secondary prevention of AD. Secondary prevention is defined here as targeting presymptomatic patients who do not have mild cognitive impairment (MCI) but have a higher risk of developing MCI and then dementia due to AD than the general population with an intervention aiming to prevent or delay the onset of a disease.[13][14] Predictive modelling is defined here as the use of data from multiple individual subjects, and statistical models to identify the likelihood of future outcomes based on historical data.[15] Ethical concern is understood pragmatically as a situation (actual or hypothetical) which requires a normative evaluation in the categories of right versus wrong.[16] Social implications are defined as consequences of actual or hypothetical choices, enacted on a societal level, which provoke a moral deliberation on the ground of ethical principles.

Our specific research questions were identified via a preliminary, targeted literature search[17] and include the following.

1. What are the ethical concerns and social implications associated with a) selection of a population for assessment of the risk of developing AD via predictive modelling? b) the disclosure of individual risk of developing AD assessed using predictive modelling in asymptomatic patients? c) conditioning of access to future AD treatment, based on the predictive modelling? d) assessment of the benefit-risk from AD treatment administered at preclinical stage, made using predictive modelling?
2. What are the broader, population-level ethical concerns and social implications of using predictive modelling tools in the setting of secondary AD prevention?
3. What other ethical concerns and social implications are raised in this context?

The current social context of these considerations is a growing pressure from patients, carers, payers and providers to develop and introduce to the market a disease-modifying treatment and therefore alleviate the current and forecasted burden due to AD. For this reason, in this review the ethical concerns which stem both from the secondary prevention approach in AD and of forsaking this therapeutic paradigm will be considered.

METHODS AND ANALYSIS
Protocol and registration
This protocol was prepared according to the reporting guidelines of the preferred reporting items for systematic reviews and meta-analysis for protocols 2015 (PRISMA-P).[18][19] The completed PRISMA-P checklist can be found in the online supplementary file 1. The review protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42018092205) on April 6, 2018. The systematic review manuscript will be prepared following the PRISMA statement. Important amendments to this protocol will be reported and published with the results of the review.

Study selection criteria
The search strategy was organised following the SPICE framework (setting, perspective, intervention, comparison, evaluation).[20]

Setting: presymptomatic AD
Studies will be included if discussing asymptomatic/pre-symptomatic individuals at-risk of AD, including those with subjective memory complaint/cognitive impairment but without MCI diagnosis. Examples of phrases that would qualify a study for inclusion are: symptomatic patients with genetic predisposition, family history or the presence of AD biomarkers, AD treatment prior to onset, cognitively intact/normal AD, prodromal AD (but only when understood as asymptomatic) and abnormal biomarkers. Studies discussing only symptomatic stages of AD or discussing dementia secondary to other diseases, or other primary dementias will be excluded.

Perspective: individual and societal
Studies reporting on both the individual and societal perspective will be included.

Intervention: secondary AD prevention using predictive modelling
Studies will be included if discussing either the predictive modelling method (statistical algorithms) or source data (genetic data, imaging data, cerebrospinal fluid examination, family data, electronic/medical health record, family history, neurocognitive assessment, demographics, etc.) as a component of secondary AD prevention, aiming to prevent or delay the onset of MCI/AD dementia in presymptomatic individuals at risk of AD. Excluded will be studies discussing secondary prevention but without any component of predictive modelling (neither method nor data source) or which do not discuss secondary prevention of AD (eg, discuss tertiary prevention which is defined as targeting individuals with MCI and later in the disease course).

Evaluation: ethical and social implications
Studies will be included if they contain discussion or commentary on ethical concerns or social implications; otherwise will be excluded.

Study type
Studies will be included if 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 will also be included, regardless of whether they were peer-reviewed or not. Animal or in-vitro studies, study protocols, and book reviews will be excluded.

Language

Only papers in English, French or German will be included.

Year of publication

Manuscripts/documents will be included if published from 2007 onwards. The choice of this time span reflects the fact that secondary prevention is a recent therapeutic strategy against AD, and therefore only relatively recent literature is expected to be relevant.

Search strategy

Electronic databases

The literature was retrieved from the following data sources: Embase/Medline, Scopus and PsycINFO chosen collectively by the group of contributors, which included an information specialist. These databases were searched in two rounds, first time on 28 March 2018 and second time from 28 May to 31 May 2018 (coverage from the beginning of time until the search date). The reason for the two rounds of search was identification of additional keywords representing the same clinical phenomenon as well as improvement of syntax strategies which allowed identification of additional manuscripts. The exact search terms used in all databases are described in the online supplementary file 2. The database searches have now been completed. Automatic deduplication was used whenever possible.

Manual search (including grey literature)

Further relevant literature, including grey literature, defined as non-peer reviewed, publicly available documents was identified in a structured manner.[21 22] First, a generic Google search engine was used and the first 10 pages of results were reviewed for potentially relevant entries. Second, a targeted search within predefined websites was conducted, using Google interface. The list of websites, compiled by one of the reviewers and then consulted within the group of contributors, included: 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/) and The Organization for Economic Co-operation and Development (http://www.oecd.org/).

Study selection

Study selection has been completed on October 8, 2018. References were managed in Excel and Mendeley. The removal of duplicates in terms of title and first author name as well as exclusion of manuscripts/documents due to the language and publication data was performed by one reviewer. The remaining manuscripts/documents were independently assessed (based on an abstract or executive summary) by two reviewers to determine eligibility. Disagreements between the two reviewers were adjudicated by a third reviewer. Manuscripts/documents were classified and described according to the reason for exclusion. Reviewers had a possibility to exclude not eligible studies based on review of the full-text versions (prior to extraction).

Data extraction

Full texts of manuscripts/documents potentially eligible for inclusion were then retrieved for data extraction. A single, qualitative review is now ongoing using a semi-structured extraction sheet developed in a form of an online questionnaire where content (text) extracted by all reviewers uploads in real time into an online spreadsheet for further qualitative data analysis.

The semistructured extraction sheet was developed in the following way: First, the following high-level sections of this sheet were predefined based on the research questions of this study and the methodologic requirements:

► Eligibility for extraction.
► Prespecified research questions
 – Selection of a population for risk assessment via predictive modelling.
 – Disclosure of individual risk assessed using predictive modelling.
 – Treatment and conditioning of treatment access, based on predictive modelling.
 – Assessment of the benefit from treatment based on predictive modelling.
 – Broader social implications/concerns at a population level.
 – Other ethical/social issues.
► Reviewer's conclusions and topics/themes to be further explored.
► Assessment of quality and relevance of a given study.

Second, each of the high-level section was populated with a specific list of ethical concerns or social implications. This list was derived by one reviewer from four studies,[23–26] selected for this purpose by this reviewer and an independent bioethicist (who is a ROADMAP collaborator but does not participate in this systematic literature review) out of a pool of around ~20 studies assessed as eligible at that point of time, based on an individual assessment as to which studies are particularly comprehensive and/or informative. Third, open-ended text boxes were added to each high-level section to allow capturing all novel themes, arguments and considerations that were not initially included in the structured list. The extraction sheet was critically reviewed within the group of collaborators and then refined.

Data analysis

Qualitative data analysis of the data extracted to date is now ongoing. The aim of this review is to provide a comprehensive landscape of the ethical concerns and social implications related to the use of predictive modelling for secondary prevention of AD. Extracted data will be analysed qualitatively using a thematic analysis[27 28] defined as 'a method for identifying, analysing and reporting patterns (themes) within data which minimally organises and

describes (your) data set in (rich) detail but also interprets various aspects of the research topic'.[21] 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'.[27] In characterising salient ethical arguments the focus is 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 will not be treated as a measure of importance.

The research questions of this study define the highest level themes. Ethical considerations, as present in the literature, will be inductively aggregated into subthemes which will lead to scrutinising, augmenting and refining the predefined highest level themes. In order to make sure that complex ethical arguments are understood in context, full-text papers will be revisited during the iterative analytic process. Multiple rounds of analysis will be conducted based on extracted data grouped in matrices of hierarchical themes and then discussed, until there is a consensus within the group of collaborators that the analysis is accurate and possibly exhaustive, given the body of evidence. Tools supporting group interpretations will be used, such as web-based analysis spreadsheets which can be accessed and modified by all collaborators in real time.

Risk of bias (quality) assessment

This is a systematic literature review conducted according to a pre-specified research protocol. Due to the qualitative character of the study objective and research questions, it aims to qualitatively understand a possibly wide spectrum of the problem and disregards the frequency with which a given ethical concern or social implication appears in the literature, which mitigates much of a possible bias in assessment of cumulative evidence. The validity and generalizability of this study lies in a rigorous methodology and the extent to which it is able to produce rich, informative description and inform further research.[29]

A potential bias might stem from some ethical arguments being missed or misinterpreted, when different reviewers appraise manuscripts and documents in a different manner. To mitigate this bias, and facilitate group interpretation, the team of reviewers participated in a face-to-face workshop on April 28, 2018 in Barcelona, during which the research objective, strategy and extraction tools were thoroughly discussed and reviewed when needed. Further to that, the reviewers involved in this study come from different backgrounds and types of institutions, thereby minimising the overall bias of selective interpretation due to a pre-existing knowledge and perspective. More specifically, reviewers 1 and 2 in this study are sociologists, reviewer 3 is a clinical psychiatrist, reviewer 4 is psychologist, reviewer 5 is a market access professional specialising in AD, reviewer is a pharmacist and market access professional, reviewer 7 is a mathematician and statistical modeller. Other contributors to the study are information specialist and a market access professional specialising in AD. All reviewers are contributors

to the Innovative Medicine Initiative project: Real World Outcomes Across the ADS pectrum for Better Care: Multimodal Data Access Platform (IMI: ROADMAP) project, in a WP8 dedicated to the ethical, legal and social implication of creating a Real World Data platform for AD research and come from a diverse background (industry, academia, patient advocacy group).

Patient and public involvement

Patients and public were not involved in the design of this study.

Ethics and dissemination

The study does not require ethical approval. The findings of the review will be disseminated in a peer-reviewed journal and presented at conferences. They will also be reported through the IMI initiative Real World Outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP).

Discussion

This systematic literature review will provide a comprehensive picture of ethical concerns and social implications which arise in the setting of AD prevention, where patients without clinical symptoms but with elevated risk of developing AD in the future receive treatment years before the disease onset. We will consider both individual and societal perspective for a possibly complete review.

Focus on the ethical and social consequences of using predictive modelling tools in AD preventive setting is a logical and necessary step in this field, which noted significant advances in the recent years with serious implications for the clinical practice. For example, recently an algorithm was developed which classifies cognitively normal patients aged at least 70 years according to their risk of developing MCI with ~70% accuracy based on routinely collected health data only.[30] The authors suggest that it could serve as a first-tier screening tool to preselect patients for a more expensive or invasive screening which would, presumably, involve genetic testing and brain imaging. Others argue that regardless of the fact that preclinical AD diagnosis was developed as a primarily scientific concept to be used in AD research, it already entered the clinical setting due to a common practice of disclosing biomarker status and the associated risk[6] and commercial initiatives offering predictive tests to a general public. To date, many of the ethical and social concerns related to AD prevention were already identified and discussed, focusing on delivery of clinical care to AD patients,[31] research ethics[32] and some specific aspects of it, such as development of readiness cohorts for AD research,[33] and using patient's genetic information for research.[34] Another topic which was widely discussed is the disclosure of genetic and biomarker risk factors to asymptomatic individuals participating in AD research.[35] However, to our knowledge, no study has explored and discussed the ethical and social implications of using predictive modelling in preventive AD setting. Given

the predictive nature of the current science in the AD domain, the technological developments in the recent years allowing to assess and potentially disclose individual-level risk assessment on a mass scale, and the outlook of future therapeutics targeting now early stages of AD continuum, including asymptomatic patients at risk, an assessment of the ethical landscape is urgently needed.

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