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Novel drug candidates targeting Alzheimer's disease: ethical challenges with identifying the relevant patient population

Erik Gustavsson [1,2] Pauline Raaschou,[3] Gerd Lärfars,[4] Lars Sandman,[2] Niklas Juth[5]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/medethics-2021-107304).

[1]Centre for Applied Ethics, Department of Culture and Society, Linköping University, Linköping, Sweden
[2]National Centre for Priorities in Health, Department of Health, Medicine and Caring sciences, Linköping University, Linköping, Sweden
[3]Clinical Pharmacology Unit, Clinical Epidemiology Division, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[4]Health and Medical Care Administration, Region Stockholm, Stockholm, Sweden
[5]Stockholm Centre of Healthcare Ethics, LIME, Karolinska Institute, Stockholm, Sweden

Correspondence to
Erik Gustavsson, Centre for Applied Ethics, Department of Culture and Society, Linköping University, Linköping 581 83, Sweden; erik.gustavsson@liu.se

Received 4 February 2021
Accepted 26 May 2021
Published Online First 11 June 2021

Linked

► http://dx.doi.org/10.1136/medethics-2021-107767
► http://dx.doi.org/10.1136/medethics-2021-107800

Check for updates

To cite: Gustavsson E, Raaschou P, Lärfars G, *et al*. *J Med Ethics* 2021;**47**:608–614.

ABSTRACT

Intensive research is carried out to develop a disease-modifying drug for Alzheimer's disease (AD). The development of drug candidates that reduce Aß or tau in the brain seems particularly promising. However, these drugs target people at risk for AD, who must be identified before they have any, or only moderate, symptoms associated with the disease. There are different strategies that may be used to identify these individuals (eg, population screening, cascade screening, etc). Each of these strategies raises different ethical challenges. In this paper, we analyse these challenges in relation to the risk stratification for AD necessary for using these drugs. We conclude that the new drugs must generate large health benefits for people at risk of developing AD to justify the ethical costs associated with current risk stratification methods, benefits much larger than current drug candidates have. This conclusion raises a new set of ethical questions that should be further discussed.

INTRODUCTION

Drugs that mitigate the symptoms of Alzheimer's disease (AD) are routinely used in clinical practice. These drugs are not disease-modifying in the sense that they alter the progression of the disease, but intensive research is underway to develop such disease-modifying drugs for AD. The aim is to develop drugs that will slow the course of the disease, for example, by postponing the onset of the disease or by slowing down the rate at which the disease develops.

In this paper, we focus on a particular track in AD research, namely, immunotherapy aimed at amyloid β (Aβ) and tau, two relevant biomarkers.[1] Antibodies that reduce Aβ plaques in the central nervous system are currently in pipeline for market approval, although a Food and Drug Administration advisory panel has raised concerns regarding the efficacy.[2] Preliminary data available at the time of writing this text indicate that the presence of Aβ in the brain decreases during treatment with these drugs. However, to what extent there are effects on cognition is still contentious.[3] When introduced on the market, many important questions will remain unanswered regarding effects and adverse side effects extending beyond the clinical trial follow-up of a few years.

A crucial characteristic of these drugs is that their intended use involves early detection of the relevant population. Therefore, these drugs raise several ethical challenges when introducing them in a healthcare system. In this paper, we analyse these challenges with a special focus on the challenges associated with treatment selection based on measures of biomarkers, which, in turn, imply that individuals need to be identified before the onset of AD.

ALZHEIMER'S DISEASE

To give the reader an idea about the intended use of these drugs, we shall, in the following, distinguish between three stages associated with AD.[i]

a. *Preclinical phase*. In the preclinical phase, the patient has no symptoms but positive amyloid biomarkers. The term 'preclinical phase' is currently an experimental concept that primarily facilitates communication in drug studies. Researchers hope to characterise a biomarker profile that represents a high risk of progression to the second phase of the disease.
b. *Mild cognitive impairment (MCI)*. It is uncertain as to how and when the preclinical phase progresses into MCI. MCI involves memory problems or other cognitive disorders that are greater than may be expected based on age and educational level, but without affecting the patient's ability in terms of activities of daily living (ADL). The symptoms associated with MCI may have causes other than AD.
c. *Alzheimer's disease dementia (AD dementia)*. In the final phase of the disease, the patient exhibits clinical symptoms with memory impairment, visual-spatial impairment and impaired language with an effect on the individual's ability to ADL.

To understand the progress of AD according to these stages presupposes an expected progression from the preclinical stage with altered biomarkers, to manifest disease. While many studies suggest that AD progresses through the stages mentioned above, [4] it is still contentious whether the disease necessarily follows this pattern.[5] However, from this perspective, the preclinical and the MCI phase constitute a 'therapeutic window' when drugs could slow down the development of the disease, for example, by reducing the amyloid burden or tau pathology. However, to use this window individuals with positive biomarkers need to be identified. In the following section, we outline ways in which this may be done.

SCREENING

Screening and testing

The strategy for identifying the relevant patient population may be organised in different ways, all of which raise somewhat different sets of challenges. Following Juth and Munthe,[6] we will distinguish

[i]We employ 'stages associated with AD' rather than 'stages of AD' since it is contentious whether some of these stages should be understood as a constituent of AD or not.[33 34]

between the notion of 'screening' and that of 'testing' where the central distinguishing feature is linked to who initiates the test.

Screening is a health examination initiated by healthcare or society that identifies certain individuals for further examination or treatment from a larger population that does not need to be combined with a preidentified or suspected increased risk (with respect to what is being examined). In the case of AD, it will be a matter of identifying presymptomatic or early symptomatic high-risk individuals for further examinations or treatments. Accordingly, throughout this paper, we shall focus on treatments that would be used in the preclinical or MCI phase/early AD. At present, the latter seems to be closest to market approval.[3]

Consider the following two forms of screening, namely, population screening and cascade screening. (1) *Population screening* are large-scale screening programmes, usually targeting people within a certain age range within a country's or region's population. Paradigmatic examples are neonatal screening or mammography for breast cancer. (2) *Cascade screening* is a more targeted form of screening, where individuals with a recognisably higher risk are offered to take a test. Cascade screening is sometimes used in genetics, where genetic relatives of a tested index person are approached with an offer to test based on the increased probability of having the relevant pathogenic variant. Accordingly, cascade screening is different from population screening, but the common denominator is that the initiative to test comes from someone other than the individual herself.

Furthermore, to take a test may also, of course, be initiated by an individual herself. Such testing may, for example, be initiated because one is concerned with the number of cases of AD in the family or because one prefers to reassure that one is not at an increased risk for developing AD. While this latter form is *testing* rather than *screening*, it may, if relatives are subsequently approached, be transformed to a question about screening.

If there were to be a treatment that reverses AD, that is, which is completely curative even when symptoms have appeared, then screening would not be needed. Then there is little therapeutic benefit with early identification and one can wait for symptoms to appear and for the disease to be diagnosed in the usual way. However, most drug candidates under development are those where presymptomatic or early identification is thought to have therapeutic benefits, and which delays the course of the disease or relieves symptoms.

Ethical aspects of screening

Wilson and Jungner[7] developed the classical criteria for when screening is justified. Without going into the details of these criteria, they can be summarised as follows: screening for a condition is only relevant if the condition is (reliably) testable, would not have been detected in time without screening, must be detected in time for the treatment to be (more) successful, the treatment is effective (enough), the condition severe (enough) and the test safe and with high predictive value. They also contain organisational criteria, for example, that the screening must be cost-effective and that there is an infrastructure for recruiting a suitable screening population and providing follow-up for those covered by the screening. Besides the Wilson and Jungner criteria, it is, in the contemporary discussion, often argued that screening programmes should also fulfil reasonable ethical standards of, for example, justice and autonomy.[6]

Population screening is aimed at a selected segment of an entire population, such as neonatal screening for all newborns or mammography for all women of a certain age. Population screening can target a population where there is no initial risk increase for the conditions being sought (as in neonatal screening) or a certain increase in risk (as in mammography where increased age means some increased risk), but usually that risk increase is low in population screening. Cascade screening is done because a person has already been tested for a condition, usually genetic, which then regularly means a calculable increase in risk for other individuals, such as genetic relatives. These individuals are then contacted as a result of the testing. In comparison with population screening, cascade screening usually involves a significantly higher and more well-determined risk for the condition in question. AD screening programmes will be somewhere between pure population screening and genetic cascade screening in terms of initial risk assessment—more on this below.

In the case of AD, less than 3% are estimated to have a strongly inherited form of the condition, so-called familial AD, and the proportion is greater among early-onset forms.[8] To some extent, these will probably be treated separately even with new drugs for AD. This is because the onset often occurs earlier for familial AD, which can lead to genetic testing with possible subsequent cascade screening. Genetic cascade screening will therefore be discussed separately, as it gives rise to special questions about, for example, insurability and contacting relatives.

Both monogenetic and multifactorial genetic biomarkers may be used to stratify the risk for presymptomatic patients outside the group with familial AD. If this is the case, the insurance issue, for example, becomes relevant for everyone in the AD screening. That possibility will also be discussed below.

From the point of view of autonomy, as screening by definition is initiated by society or healthcare rather than the individual, there is always the problem that screening means more or less pressure to accept the offer of testing since those who offer screening often are considered as authorities in medical issues, by those to whom the screening is offered, and that they thereby have a reason to accept the offer if made.[6 9]

It also means that screening increases the risks of unnecessary anxiety and overtreatment compared with regular healthcare. These risks are also increased by screening at a presymptomatic or early symptomatic stage, which will be developed in the following. Traditionally, therefore, screening has been considered justified only if there is a treatment with a well-established effect.[7] In addition, there must be proven and clear treatment benefits with identifying the condition at a presymptomatic or very early stage. Accordingly, the ethical tension regarding screening boils down to, on the one hand, benefiting people at risk for disease in terms of health, and on the other hand, respecting and promoting these people's autonomy.

In the next section, we shall discuss seven scenarios for risk stratification and selection of patients for treatment. In the Population screening for AD section, we discuss traditional population screening without genetic biomarkers. In the Population screening with genetic testing for AD section, we focus on traditional population screening with genetic biomarkers. In the Early identification of AD patients without population screening section, the focus is on early identification of AD patients without population screening. In the Genetic cascade screening section, we discuss genetic cascade testing for AD.

DIFFERENT KINDS OF SCREENING: ETHICAL ASPECTS

Population screening for AD

If an effective drug that targets the preclinical phase receives market approval, the question of population screening may be actualised. One way to identify the relevant population is to screen for AD in the same way as screening is available for, as in several OECD countries (the Organisation for Economic

Co-operation and Development), breast cancer (mammography): that everyone at a certain age is contacted with an offer of testing and possible follow-up.

To implement such a population screening programme for AD, several decisions need to be made. First, the age for screening must be determined (of course, screening can be performed repeatedly, with more ages having to be determined). Second, the method of risk stratification (the test method) for AD must be determined. Third, follow-up for those who are deemed relevant for further investigation and treatment must be determined. Fourth, an organisation and infrastructure to implement and follow-up on all this must be formed. All these steps are of course connected: what, for example, is a suitable age relates to when the condition in question can be reliably identified and when the treatment gives the best effect.

Starting with the age decision, there is a built-in conflict here between, on the one hand, initiating treatment as early as possible (so that the presumed benefits of early treatment are as large as possible) and, on the other hand, avoiding false results with the problems it entails (the earlier the risk stratification, the more uncertainty).

For example, consider the difference between population screening for AD at age 65 and age 85. At age 65, only a minority of those ultimately diagnosed with AD have been diagnosed. This is an advantage to the extent that early detection is an advantage for treatment. However, this advantage is not greater than the *extra benefit* that early screening-induced diagnosis entails. The relevant comparison is therefore not between treating AD and not treating AD, but between treatment of AD as a result of the screening and the treatment that would still have been carried out without the screening.

Already at this point, it should be emphasised that it is very unlikely that a significant proportion of individuals with familial AD would benefit from population screening. Familial AD is often detected via an index person, which causes cascade screening of genetic relatives who also may carry the pathogenic variant. Accordingly, the index person would often be identified at a younger age than any screening programme for AD would be relevant, as the onset of familial AD usually is earlier than for other AD.[8] Accordingly, individuals are often aware of the familial risk in families where familial AD occurs long before the benefits of early identification via population screening would be relevant.

Early identification (eg, at the age of 65) entails a great risk of false results, especially for false positives (ie, those who are incorrectly diagnosed as having the condition in question even though they do not have it).[10] False positives naturally cause unnecessary anxiety, with the negative impact on quality of life that this may entail. This concern can be significant: studies indicate a greatly increased risk of suicide when diagnosed with serious neurological conditions and other potentially life-shortening conditions, such as cancer or Huntington's disease.[11–14]

Furthermore, false positives can result in overtreatment. Overtreatment is a significant harm from several points of view. First, there are few drug treatments that do not have adverse effects. For example, the clinical trials of antibodies targeting AB-amyloid oligomers which could receive market approval within a few years have revealed a rather high percentage of amyloid-related imaging abnormalities with edema (ARIA-E) or microhaemorrhage (ARIA-H).[15] Overtreatment means by definition that the benefits of the treatment are absent while a subset of those treated experience side effects. Second, treatments often cause different types of burdens that involve both the patient and the relatives, with, for example, care visits and care measures. Third, all this means that resources are used, which means an opportunity cost in terms of other patients' health as the resources could have been used for other care instead.

As mentioned above, for AD, currently, the link between the preclinical phase or MCI and manifest AD is still associated with uncertainties. Moreover, the time between the asymptomatic phase (which could be detected with screening) and clinical symptoms of AD may be so long that the patient in question die due to other causes before the disease gives rise to any problems.[16 17] The same applies, for example, to PSA screening for prostate cancer, where only a minority of those who are ultimately identified via the screening as prostate cancer cases and treated would have had their lives shortened by prostate cancer.[18] In other words, even true positives can lead to overtreatment. This also goes for AD identified presymptomatically: most people with preclinical AD will die without having clinical symptoms of AD. For example, a 60-year-old woman with preclinical AD has only a 30% risk of developing AD, that is, 70% die of other causes before symptoms appear.[10]

In other words, the proportion of overtreated people would probably far exceed those who are correctly identified by means of early screening at the age of 65 and who would have a treatment advantage from the screening.

Because the preclinical test methods are uncertain at an early age, they would also give false negative results, that is, that those who eventually develop AD are not identified; a generally unreliable test gives rise to both false negatives and positives.[18] False negatives, in turn, lead to false security with an associated risk of not looking for symptoms. The worst-case scenario is that correct diagnosis and treatment may be delayed by believing that the diagnosis is already ruled out.[6] Such concerns have been expressed about, for example, mammography.[19]

To avoid false positives and negatives, the screening can be initiated at a higher age where the risk of false results decreases, as a larger proportion of those who will actually develop AD have already started to show identifiable symptoms, say at the age of 85. However, the advantage of early identification then decreases, which was the very motivation for population screening in the first place. Hence, in the absence of significantly more reliable methods for early risk stratification and effective drug treatments, population screening for AD seems difficult to justify.

Furthermore, screening requires an organisation and an infrastructure that require resources. This is also true for more limited programmes for early identification of AD (see below). It is not just the testing itself and possible follow-ups in terms of further examinations and treatment that demands resources. In population screening, there must be an organisation to call participants and book appointments for everyone in the current age segment, to meet them and obtain informed consent and to follow-up and evaluate the screening as a whole. Some screening programmes, for instance, neonatal screening in countries such as Sweden, Norway, and the UK, may piggy-back on the infrastructure of neonatal care (at least to some extent), as most women in these countries give birth in a publicly run care facility. This advantage does not exist for population screening for AD (although some high-risk screening could possibly use, eg, primary care—see below).

Let us illustrate this with a simple arithmetic exercise by using the Stockholm region in Sweden as an example. If population screening for AD is introduced, a separate infrastructure would need to be built that recruits the approximately 10–11 000 people who turn 65 each year in Stockholm. If we allow extrapolation from American data, then these indicate that about 11%

of all Americans over the age of 50 have about 30% elevated levels of beta-amyloid and meet the criteria for preclinical AD.[20 21] Given that common methods for preclinical risk stratification are used in Stockholm, approximately 10 000 people will thus need to be screened for AD annually in Stockholm alone, of which approximately 1000 (with a conservative estimate) will be identified as preclinical cases which will then be subject to further investigation and possible treatment. In a 10-year period, 10 000 new patients with AD will be added, which demands further resources. Again, a minority of these (about 30%) will actually develop AD. Then, we have not taken false positives or negatives into account.

To summarise, population screening for AD is associated with several ethical problems. There are general problems with screening regarding, for example, autonomy and causing potential anxiety. Furthermore, there are the problems associated with current methods for risk stratification being unreliable, resulting in false negatives (with risk of undertreatment) and, above all, false positives (with risk of overtreatment). As seen above, the risk of overtreatment is considerable given current uncertain risk assessment methods. Accordingly, population screening for AD cannot be justified, at least not currently. However, if a very effective drug targeting the preclinical phase becomes available, or if much better methods of risk stratification are developed, the question about population screening may need to be reconsidered. Moreover, as will become clear in the following, the discussion about population screening for AD is relevant to take a position on more targeted methods for risk determination.

Population screening with genetic testing for AD

To make the risk stratification of AD more reliable, genetic testing could be added. This seems to be the idea behind some drug trials that make use of combination therapy for individuals without cognitive impairment but with a pathogenic variant in a gene which increases the risk of AD, for example, *ApoE4*. However, *ApoE4* should not be confused with the highly inherited familial form of AD mentioned above. Familial AD is often dominantly inherited, that is, it is enough that one of the parents has the variant for the child to have a 50% probability of getting the pathogenic variant. Furthermore, the penetrance is almost 100% in familial AD, that is, if one has the variant, the disease almost certainly breaks out. *ApoE4* is neither dominant nor particularly penetrating; however, it entails a certain level of increased risk and is one of several possible biomarkers that together can provide a risk assessment.

The advantage of including testing for pathogenic variants in *ApoE4* (or other known risk genes) in general screening programmes is thus that it can make the risk determination more reliable.[22] However, there are several disadvantages. One is that standards for informed consent are usually higher when genetic testing is involved, compared with standard screening programmes.[23] Such standards may be reasonable, but they also require healthcare resources, as they require trained staff to communicate comprehensible and relevant information to the participants in the screening programme.

Furthermore, jurisdictions in several countries (eg, the Netherlands, Sweden, parts of the USA) allow insurance companies to be given some access to genetic information.[6] According to such legislation, if the insurance company requests genetic information given certain circumstances, the person is obliged to account for it; otherwise, it is considered a breach of contract and the insurance is invalid. In other words, genetic testing means that you can obtain personal insurance to a lesser extent, since insurance companies can increase the premium or refuse insurance based on the genetic risk information about a person.

In view of these problems with genetic analysis, the benefits of added diagnostic precision and treatment effect must be significant for it to be justifiable to include such. This does not apply to *ApoE4* analysis today.

Early identification of AD patients without population screening

Following the classification spelled out above, AD is associated with three stages: the preclinical phase. the MCI phase and the AD phase (when the diagnostic criteria are met). These stages constitute three possible points in time where AD may be identified and treated. In the following, these are discussed in turn.

The preclinical phase

Clinical trials that include individuals in the preclinical phase are building on the hypothesis that there are treatment benefits with early identification and treatment. Given that population screening is currently ruled out, when it comes to identifying the preclinical potential treatment group, there are three possibilities: (1) screening of high-risk groups, (2) that individuals seek care themselves to be tested due to worry or (3) that certain care providers (eg, primary care physicians) offer examination on their own initiative (so-called opportunistic screening).

Let us start with option (1): screening of high-risk groups for AD (hereafter high-risk screening). High-risk screening means that there is already some form of risk stratification that points out the target population. For example, screening of those who have been diagnosed with a known increased risk of another disease (ie, comorbidity) and who are then screened for this other disease, for example, screening of patients with long-term hepatitis for liver cancer.

There are several ways in which such high-risk screening can be organised. One possibility is that everyone who makes a primary care visit over the age of 75 is offered an investigation (eg, a combination of a memory investigation and biomarkers or only the former). Another possibility is that everyone (or any suitable subgroup of everyone) who encounters geriatrics is offered an investigation.

It is important to point out that regardless of the approach, there is still a difference between population screening and high-risk screening. The current focus is not on, for example, all 75-year-olds in a region being contacted by healthcare and offered an investigation for AD. To adopt such a policy is to introduce population screening for AD for 75-year-olds. Then the above reasoning about population screening for AD is applicable.

The current focus is the possibility of regularly offering a clinical workup for AD to those who apply for or end up in primary or geriatric care (at a certain age) for other reasons than being concerned with symptoms associated with AD. A possible advantage of such an approach could be that the probability assessment that the patients in question develop AD is more reliable (compared with population screening for AD). However, it is not certain that those who seek primary or geriatric care have a greater and more well-determined probability of developing AD compared with people of the same age in the population as a whole. In any case, there are currently no studies that show that this is the case. Therefore, these two possibilities are high-risk screening in the sense that people above 75 and patients at geriatric clinics have an increased risk in relation to the general population as a whole but they are not at higher risk compared

with people above 75 who does not happen to end up in primary or in geriatric care.

It is also important to point out that all disadvantages that come with population screening come with high-risk screening. The problems of autonomy and anxiety are the same (although more limited in volume) for the same reason: the initiative for testing still comes from healthcare, regardless of the reason for the visit. In the absence of studies supporting a more well-defined probability in high-risk screening, there are also the same problems with overtreatment and false results as in population screening (although the volume will be more limited).

Option (2) would not involve any difference from what is already taking place in healthcare today: if people have sufficient concerns, an investigation for AD can be initiated. Unless deliberate attempts are made to increase people's concern for AD, it is unlikely that a large proportion of the total population will seek investigation for AD in a preclinical phase; by definition, they lack symptoms to worry about. Therefore, option (2) does not raise any specific ethical issues regarding the identification of individuals at risk for AD.

Alternative (3), that healthcare professionals on their own initiative to a greater extent propose an investigation to identify people with preclinical AD would be best described as having started so-called opportunistic screening, which generally has more disadvantages than organised screening. First, opportunistic screening reinforces arbitrariness and inequality: it is those who *happen* to receive the offer who benefit from the potential advantages (or suffers the disadvantages) of testing, but not others. Second, opportunistic screening entails a lack of follow-up and evaluation of the screening's benefits and risks compared with organised screening, where organisational requirements for evaluation are included. Overall, opportunistic screening for AD is thus probably even less desirable than population screening.

The MCI phase

Clinical trials that include individuals with MCI (as well as early AD) are associated with similar problems as those aiming at the preclinical phase as lack of precision in current methods of risk stratification make MCI (as a symptom) in combination with biomarkers an unsuitable test method for screening. Therefore, it seems quite unlikely that high-risk screening would identify a larger proportion of the individuals at risk for AD.

There are also studies suggesting that the presence of biomarkers already today increases the probability that drug treatment is initiated at MCI, despite the fact that evidence for a good treatment effect is weak.[24] This suggests that there is a risk of indications shifting regarding drug treatment of early suspected AD, which is a reason for caution regarding early identification.

The clinical phase: AD

Some of the ongoing clinical trials are looking at drugs that target a population with established AD. The closer to the clinical phase, the more irrelevant the question of different methods of risk stratification becomes as those in need of treatment are likely to contact healthcare due to symptoms (in the usual way). Therefore, we are still facing the dilemma mentioned above: the earlier identification, the more unreliable identification of true AD cases. The later the identification, the less potential treatment benefits compared with standard diagnostics as it goes to today. Overall, there are weak reasons to believe in large treatment benefits with early identification. This is what would be needed for large risk stratification for AD to be justified.

Accordingly, there are basically the same problems with screening of high-risk groups in the preclinical phase and MCI phase as with population screening. In addition, there are problems of inequality and arbitrariness. When the clinical phase begins, there is no point of screening: the later the identification, the less potential treatment benefits compared with standard diagnostics.

Genetic cascade screening

Genetic cascade screening: familial AD

Familial AD is the directly inherited form of AD. Less than 3% of the total number of AD cases are familial.[8] Familial AD usually debuts earlier than AD in general: often before the age of 65. Familial AD is normally autosomal dominant, that is, not gender-specific (affects both women and men) and a predisposition from a parent is sufficient for getting the disease. The probability of getting familial AD is thus (approximately) 50% if one has a parent with the predisposition and the penetration is (almost) 100%.

The pathogenic variant can be identified by presymptomatic genetic testing. The variant is present and can in principle be found from the embryonic stage. Normally, tests are performed only if family history (or relatives diagnosed via genetic testing) gives reason to suspect predisposition. It is not known for sure, but about 20% of those who know that they have a familial risk of familial AD also choose to do a genetic test.[25] Similar numbers apply to presymptomatic tests for Huntington's disease.[26] Overall, both in terms of the nature of the disease, genetics, lack of treatment and how the diseases are managed in genetic counselling, there are clear similarities between Huntington's and familial AD.

There are no known medical benefits today with presymptomatic genetic testing for familial AD, as no treatments prevent or delay onset. Familial AD is still tested presymptomatically by those who request it and where there is a suspicion due to family history. There are two types of reasons to offer testing, despite the lack of medical advantages: to reduce anxiety (some prefer to know, even if one is a carrier of the pathogenic variant, rather than remaining uncertain) and to promote autonomy. The rationale for promotion of autonomy of the test subject (index person) is roughly as follows: if one knows that one will (or will not) suffer from a certain severe and life-shortening disease, one can plan one's future in accordance with how one wants it to take shape. If, for example, one knows that one has a predisposition for familial AD, one may not invest in a long education in the middle of life or one may consider fetal diagnostics in family formation. To achieve these potential benefits, however, extensive and individually tailored genetic counselling is required, which is a lengthy decision-making procedure with several steps and patient meetings.[27 28]

As indicated above, these arguments for offering presymptomatic testing to individuals who already suspect familial risk and who themselves request it are not applicable as arguments for *screening*. Screening rather risks undermining autonomy and increasing anxiety: those who are contacted via screening often have no idea that they may be at risk for the disease in question and that there is something to worry about. Regarding such strongly hereditary conditions as familial AD, it is also unlikely that one is not aware of the risk of being affected from the beginning. Those who have not applied for testing themselves can therefore to a large extent be assumed to be uninterested in this. For these reasons, among others, cascade screening should be handled with caution when it comes to familial AD. Indeed, genetic cascade screening for familial AD would be more

justified if there was a treatment with preclinical medical benefits. Then familial AD would be more analogous to testing for, for example, *BRCA1* in familial breast cancer, for example, than to Huntington's. The *BRCA1* variant carries a greatly increased risk of breast cancer (approximately 60% probability of onset during a lifetime), but there are preventive measures such as monitoring and prophylactic mastectomy, which significantly reduce the risk of disease onset. There, genetic cascade screening is normally encouraged with identified predisposition, precisely because there is a clear medical benefit with presymptomatic knowledge.[27]

Even when there are preventive measures, there are of course ethical issues regarding genetic cascade screening.[27 29] First, there are the possible psychosocial consequences in terms of, for example, insurability and discrimination, which have already been mentioned above. Second, treatability is a matter of degree: completely curative treatments are unusual, nor would it be the case with the AD treatments that will be offered in the foreseeable future. Third, there are always more or less large adverse side effects and treatment burdens; as mentioned above, this also seems to be the case for new AD drugs.

Furthermore, there are a number of ethical questions relating to contacting relatives who may be unaware that they are potential carriers: when and how should they be contacted, who should contact, etc? There is an extensive literature on these problems that shows the advantages and disadvantages of different solution proposals.[27 30 31] To fully discuss these complex issues is beyond the scope of this paper. More importantly, regardless of how these issues are tackled, screening for familial AD does not bring anything new in principle to these issues that give rise to a reconsideration of established practice.[27]

The question is instead precisely whether such cascade screening should increase in scope given that one of the new early-stage drugs is approved for use. The discussion above suggests that this should be the case if it turns out to have a preclinical treatment benefit for this particular group. The latter factor is crucial, there are indications that familial AD works differently (eg with other causal mechanisms) than other types of AD. Therefore, it is far from certain that documented effective treatment for AD in general is also effective for familial AD.[32] This must be examined separately. However, if sufficient preclinical treatment benefits (compared with disadvantages) of a particular treatment for familial AD have been established, then genetic cascade screening may be warranted. Note, however, that this refers to a very limited group of patients.

Genetic cascade screening: *ApoE4*

In this section, we focus on testing genetic relatives when an index person has already been identified with genetic risk markers for AD. There are about 20 known genes that affect the risk of AD. The one that has found the greatest individual impact is *ApoE* and in particular *ApoE4*. There are various estimates as to how much the risk increase is given to this variant (from 1.5 to 4 times the average lifetime risk). In the presence of double alleles, the risk increase is 10–12 times higher. A person's risk profile is further modified by variables such as age and other genetic factors (in addition to *ApoE*). However, as an isolated risk factor, it is considered too limited and unreliable to have clinical relevance.[22] There are no serious agents (outside the commercial sector—those who sell these tests are of course of a different opinion) who have suggested that genetic cascade screening should be introduced based on this or any of the other risk-affecting variants. Given the current state of knowledge, this possibility can thus be set aside, at least for the time being.

To sum up, if there is a preventive and effective treatment that is effective against familial AD specifically, genetic cascade screening can be defensible for this group. In that case, the best practice procedures for genetic cascade screening should be followed, whatever that may be. However, it is a small proportion of the total number of cases of AD. Genetic cascade screening for risk genes in multifactorial AD is not defensible.

CONCLUSION

Population screening for AD is associated with several problems. There are general problems with screening from, for example, the point of view of autonomy. But there are also problems related to the current methods of risk stratification being unreliable, which, in turn, results in false negatives with risk of undertreatment and, with a larger magnitude, false positives with risks of overtreatment and anxiety. High-risk screening has (in addition to the problems related to population screening) problems with inequality and arbitrariness. When the clinical phase begins, the point of screening is lost: the later the identification, the less potential treatment benefits compared with standard diagnostics as it is today.

We conclude that the new drugs must generate great health benefits to justify the ethical costs that come with current diagnostic methods. However, what 'great health benefits' amount to more specifically needs to be further analysed. If, and if so in what ways, benefits should be aggregated over the patient population as a whole and if, and if so in what ways, the relevant sense of health benefits involve benefits accruing to the patient's family and friends or solely to the individual at risk for AD are questions that seem particularly pressing. These questions will be further explored in a future paper.

Contributors EG drafted the manuscript, while NJ made several crucial substantial contributions. GL, LS and PR all critically revised and approved the final version of the manuscript.

Funding This study was funded by Stockholm County Council.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Erik Gustavsson http://orcid.org/0000-0001-5448-9209

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