Response to review comments (medethics-2021-107304)

Reviewer: 1

Congratulations on writing a very clear paper on a potentially complicated topic. I don't have much to say since I was impressed by the clarity and by the arguments.

Nevertheless (!), you might wish to highlight a little further some of the nuanced difficulties associated with the science of Alzheimer's disease (AD) at the moment. There is the old problem of distinguishing AD from normal ageing at the early, especially at the pre-clinical, stages. Normal older (and younger) people can have amyloid in their brains. You must stay well clear of suggesting that amyloid equates to disease in any simplistic manner. As you will know, a combination of biomarkers, including the detection of amyloid, can have a high positive predictive value vis-a-vis AD, but it is not 100%. You make this point, but you also still talk about "investigating for AD", whereas the investigations you are talking about are for amyloid or for other biomarkers of AD (which may nor signify AD). As you say, for instance, there are other causes of MCI and it might be, in any case, that MCI "caused" by AD already presents a stage that is too advanced for treatments to work. These uncertainties, when touched upon, are well worth emphasising. And at the start, it's worth emphasising further that there remains great uncertainty about the efficacy of the new drugs (and the efficacy of the old drugs is only modest), so the whole question of screening seems irrelevant. Your paper is still timely, but the levels of uncertainty could be made more apparent perhaps.

Author response

We have made these important clarifications in the revised manuscript in the following places:

- “Introduction” – second paragraph

- “Alzheimer’s disease” – final paragraph

- “Population screening for AD” – eights paragraph

- “Early identification of AD patients without population screening” – sixth paragraph

Finally, is there a way to word the Conclusion so that the reader is not left in such anticipation? Perhaps you could be more positive: there is still a question about "great health benefits", which would have to consider the following questions (x, y and z) and to which we hope to return in a later paper. The final "however" sticks out a bit like a sore thumb and could be more naturally included earlier in the sentence.

Author response

In the revised manuscript we have shortened and revised this part of the conclusion in this regard.

Reviewer: 2

This paper identifies an important issue in the context of emerging treatments for Alzheimer’s disease: how can we best identify those patients that might benefit from novel treatments before they have developed symptoms? With a few minor revisions the paper will absolutely be worthy of publication.

The central argument of the paper seems to be that emerging drugs for Alzheimer’s are most likely to be beneficial (or have the most potential benefit) if administered early, but the means of identifying

patients in these early stages present various ethical problems. While I am sympathetic to the argument as a whole, there were a few aspects that I wasn't sure about.

Author response

We believe that his is a fair description of the central argument of the paper.

First, the authors argue that a general problem with screening is its impact on patient autonomy. The suggestion seems to be that an offer of a test initiated by the health system places pressure on the person to accept, thereby undermining their autonomy. It is not clear to me why offering a test creates pressure to accept it, however. Perhaps offering a test makes people more likely to accept it (by making it a live option for them), but this doesn't make the choice to accept the test any less autonomous. Conversely, if the offer of the test reveals something about the person's health that they would prefer not to know, offering the test can undermine autonomy by (indirectly) giving them information they do not want; this violates their freedom 'not to know.' Maybe this applies to cases of high-risk screening, but doesn't seem to be a problem of screening in general.

Author response

We are prepared to stand by the judgment that screening implies pressure to accept the offer and represents a problem from the point of view of autonomy. In the revised manuscript we revised this paragraph to make this point clearer. We also added a reference where the argument has been convincingly made in fuller detail. Elton, L. (2020). Non-maleficence and the ethics of consent to cancer screening. *Journal of Medical Ethics*.

Second, the authors seem to suggest that there isn't anything wrong with people seeking out testing on their own (Option ii on page 14). Of course, such testing risks false positives or false negatives as well, and the accompanying harms of over or under-treatment. Why are the risks of these harms acceptable at the individual level, but not the group level? This suggests that the main worries arising from over or under-treatment are resource allocation concerns, rather than harms or benefits to the patient.

Author response

The issue we want to highlight is the ethical dimension of by whom the testing is initiated and in discussing option (ii) we wanted to highlight that option ii does not differ in this regard from how things are done today. We have tried to clarify this in the revised manuscript.

Third, the authors give two possible approaches to high-risk screening (all patients 75+ who make a primary care visit, and those who encounter geriatrics). They state that the weakness of such an approach is that it is not clear that these populations would have a greater or more well-defined probability of developing Alzheimer's disease. If this assumption is true, this doesn't seem to be an example of high-risk screening at all. Is the argument that high-risk screening cannot be done for early Alzheimer's, because there are no sufficiently reliable risk markers? I'm not sure this has been shown (the examples don't show this). Or is the argument that in order for high-risk screening to be justifiable, the risk factor needs to be of a certain reliability (which is not met by the examples) in order to justify the resources of a screening program?

Author response

The point we want to make is that 75+ in PC and visitors to geriatrics may have an increased risk in relation to the general population as a whole but not in relation to 75+ who does not happen to end up in PC or in geriatrics. We have clarified this point in the revised manuscript.

A fourth minor point: The authors seem to primarily be considering drugs that would provide benefits in the early stages of disease (pre-clinical and mild cognitive impairment). While this is made clear later on in the paper, it would be useful to state this focus earlier on.

Author response

It is correct that the drugs that we are considering target the early stages. We have clarified this point in the fourth paragraph of the introduction.