Reviewer's report

Title: Advance directives as a tool to respect patients' values and preferences. Discussion on the case of Alzheimer's disease.

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Reviewer: Esther Lee Marcus

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I read the article with great interest. It is a well-written thought-provoking article that gives an in-depth discussion of the various aspects of advanced directives in patients with Alzheimer's disease. Specifically, I found that the discussion about the spectrum between pre-dementia and various stages of dementia and decision-making on the one hand and using advanced directives on the other hand, excellent. The discussion about advanced directives and participation in research is very important, since it is often neglected.

I have some comments and suggestions that may enrich this discussion.

In the Background section the author presents an excellent brief summary on the change in diagnostic criteria for Alzheimer's disease and early diagnosis at the mild cognitive impairment (MCI) or predementia/prodromal stage, including the role of various biomarkers. Apart from the issue of the role and appropriateness of advanced directives in the early stages of Alzheimer's disease, a related medical ethical issue is the potential effects of diagnosis disclosure on the patient. For example, in a review article titled "To know or not to know: ethical issues related to early diagnosis of Alzheimer's disease (Mattsson et al. International Journal of Alzheimer's Disease 2016;Article ID 841941) the authors discuss the various aspects of this issue "A test result indicating AD may bring extended followup and stigmatization resulting in feelings of hopelessness, agony, and despair" (Page 2). The diagnosis can cause depression, and maybe an increased risk of suicide. (Although the link between increased risk of suicide and the stigma of diagnosis is not clear). The article mentioned above also addresses the issue of advanced directive and can be added to the reference list. Another excellent review of this subject is the article by Gauthier S et al "Diagnosis and management of Alzheimer's disease: past, present and future " (Progress in Neurobiology 2013;110:102-113): "Those arguing against the practice of disclosure also evoked the potential for adverse psychological reactions, including anxiety, depression (Maguire et al., 1996), and catastrophic thinking (Thompson et al., 1990). Suicidal ideation (Rubin and Kinscherf, 1989 ; Draper et al., 1998) as well as suicide (Markle, 1993; Frierson, 1991 ; Draper et al., 1998) were also cited as concerns, though a growing body of evidence suggested that comorbid depression, as opposed to AD, was the driving factor in the case of reported suicides (Rohde et al., 1995). Moreover, despite the association between the transmission of diagnostic information—and consequent "confrontation with cognitive deficits" (Meyers, 1997)—and depression, the claim was made that the argument for long-term
psychological sequelae was empirically unfounded with the risk of lasting psychological damage mitigated by the use of psychological defense mechanisms—including externalization, displacement, and somatization (Bahro et al., 1995)—and neuropsychological deficits in the form of anosognosia (Michon et al., 1994)". I think that the author should refer to this issues in the Background section since diagnosis disclosure is the first step before considering advance directive in this population." (Page 104).

Another issue is the statements about the value of biomarkers in early diagnosis. The author should emphasize more the limitations of those biomarkers and the predictive role of MCI and that there is still a possibility of an erroneous test as discussed by Mattsson et al "However, even a test with ad diagnostic accuracy of 90% results in a large number of misdiagnosed persons if the disease prevalence is 50%, which is the typical prevalence of AD in MIC cohorts"(page 2).

Regarding the issue of personhood in dementia (Pages 4-6, the argument of personal identity) I would add referring to the reports in the literature about people with advanced dementia who respond to music, and are able to use artistic and creative skills (For example: Crutch and Rossor "Artistic changes in Alzheimer's disease" International Review of Neurobiology 2006;74: 147).

In " Ethics of the Fathers 2:4 it is claimed "Do not judge your fellow until you have stood in his place". In the case of a patient with dementia one may claim: do not judge yourself until you have stood in your place when you suffer from dementia. On page 8 the author claims "On the contrary, although the disease may appear in slightly different ways and time of progression in different patients, AD has a quite well known course that can be communicated to the patients". Although the course can be communicated to the patient, we do not really know what are the feelings and emotions of people in advance dementia, do they suffer, and as a consequence it is difficult for a patient with pre-dementia or mild dementia to know and anticipate what he/she will want when they are in advanced stage of dementia. (See discussion about that gap of knowledge about the feelings and what is the live experience of being in advance dementia in an article we recently published (Marcus EL et al. Ethical issues related to end of life treatment in advanced dementia: The case of artificial nutrition and hydration. Diametros 2016; 50: 118-137).

On page 15 the author suggests "Nevertheless, as we have argued, current interests should not override the indication of a clear and not too broad advance directives, and the values of others should not prevail over the patient's values, as they do not prevail in the case of a competent person". However in the Abstract and also in the text the author supports advanced directives that contain the appointment of an attorney. It has been shown that surrogate decision-making is complex and in many times reflects the attitude and opinion of the attorney and not the wishes and attitudes of the person. I think that the author should clarify this issue further.

Page 12, line 17 "May wish to terminate life-saving treatments including nutrition and hydration". Do you mean artificial nutrition and hydration? or even oral feeding?
Another issue that may be discussed in barriers to implementation of advanced directives. In the article by Spoelhof and Elliot (Implementing advance directives in office practice (American Family Physician 2012;85:461) the authors discuss barriers to implementation of advanced directives. Among those barriers are: health literacy (which may be more prevalent among patients with pre-dementia or early stages of dementia), difficulties in understanding end-of-life terminology and spiritual, cultural and racial traditions. I think that the author should refer to these barriers, in brief, with emphasize on specific issues relating to patients with AD.

To the general discussion about the role of advanced directives in Alzheimer's disease I would suggest that the author can refer also to the article by Burla et al. "Alzheimer, dementia and the living will: a proposal (Med Health Care and Philos 2014;17:389-395).

Another issue related to advanced directives in general in in dementia patients specifically is that patients change their mind with time. Jongsma et al in their article "The implausibility of response shifts in dementia patients ( J Med Ethics 2015) discuss the differences in wishes of dementia patients that do not conform or contradict earlier expressed preferences. This may lead us to sometimes disregard prior preferences even when expressed in advance directives. The authors (Jongsma et al) argue that because of the loss of cognitive capacity this change in preferences is not a result of change in perception and evaluation of quality of life that caused a "response shift", and therefore a change in expressed wishes should not be followed blindly. The author may add to her discussion those concerns.

In summary, I think that this article can contribute to the care of dementia patient in various stages of dementia and influence health-care teems, and policy-makers.

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