Predictive modelling for secondary prevention of Alzheimer's Disease: Ethical concerns and social implications based on targeted, narrative literature review.

Zuzanna Angehrn[b], Hélène Karcher[b], Frédéric de Reydet de Vulpillieres[a], Clementine Nordon[b]

[a] Novartis Pharma AG, Basel, Switzerland, [b] Analytica Laser

Poster #PND46
presented at ISPOR
Baltimore,
May 2018

Background

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 "at-risk" individuals. These individuals do not have Mild Cognitive Impairment (MCI) but their levels of AD biomarkers are elevated.

They key feature of AD prevention is the need to intervene with a treatment years (or even decades) before the onset of cognitive, behavioral or functional declines (Visser&Tijms 2017), without having a sound understanding of the natural history of the disease and associated causal mechanisms.

Therefore predictive modelling--defined as the use of statistical techniques on data from multiple individual subjects to identify the likelihood of future outcomes based on historical data--(Waljee 2013)) is necessary in this setting. Such an approach raises multiple ethical issues and social implications.

Objective

As part of the European ROADMAP Consortium, we have set-out to map the ethical concerns and social implications raised by the use of predictive modelling tools in the setting of secondary prevention of Alzheimer's Disease.

Methods

A targeted, narrative literature review was performed in Nov/Dec 2017. Peer-reviewed publications were identified in PubMed or using a snow-ball approach and included when meeting the following eligibility criteria:

Setting: pre-symptomatic AD (→ with elevated biomarkers of AD or Subjective Memory Complaint but before MCI diagnosis)
Perspective: individual and societal
Intervention: secondary prevention with use of predictive modelling (→ technique or input data)
Evaluation: ethics (→ethical commentary is present/implied)

Ethical/social themes were mapped using qualitative content analysis based on analysis of full-text publications.

Results

Seventeen papers were identified as eligible, read in full and analysed. The following ethical issues and social implications were identified along patient's journey:
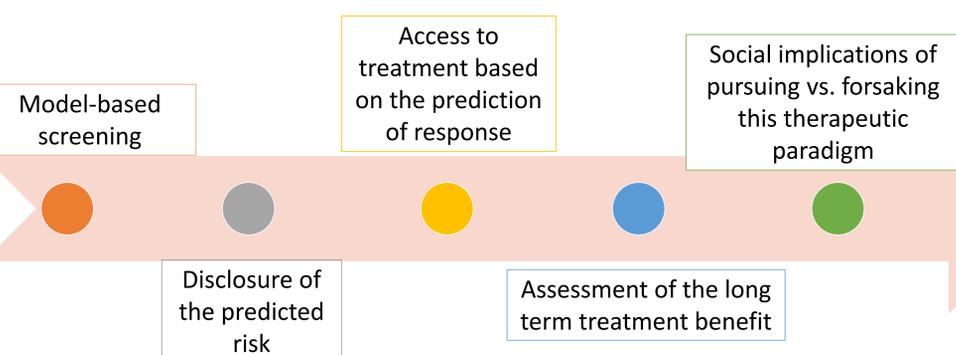

Figure 1. Ethical issues and social implications of AD prevention using predictive modelling tools

1. Given that population-wide treatment might not be appropriate (side effects, budget impact), how to identify the at-risk population (population based screening vs. targeted screening, if the latter – who should be screened?). How to assure privacy and security of personal/medical data used to assess to the risk?

2. How, when and to whom disclose the model-based individual AD risk, given the inherent uncertainty (false positive/negative)? Can the results of the risk assessment be withheld from patients given their right to be informed (and that they could act on this information for their own benefit by changing the life style, making legal and care provisions for the future, etc.)

Results cont'd

3. Who should receive the future preventive AD treatment (all, all at-risk, those with the highest risk, those in whom the anticipated treatment effect will be the largest)? Can individual's access be conditioned based on results of a predictive model? How will the risk assessment affect patient's access to other, non-AD related health services (purchasing insurance, becoming a transplant recipient, etc.).

4. What level of uncertainty in estimation of the individual benefit-to-risk, cost effectiveness, and overall societal benefit from preventive treatment is acceptable, given that future Phase 3 trials will conclude on some but not all meaningful outcomes (e.g. cognition vs function and dependency)? See Figure 2.
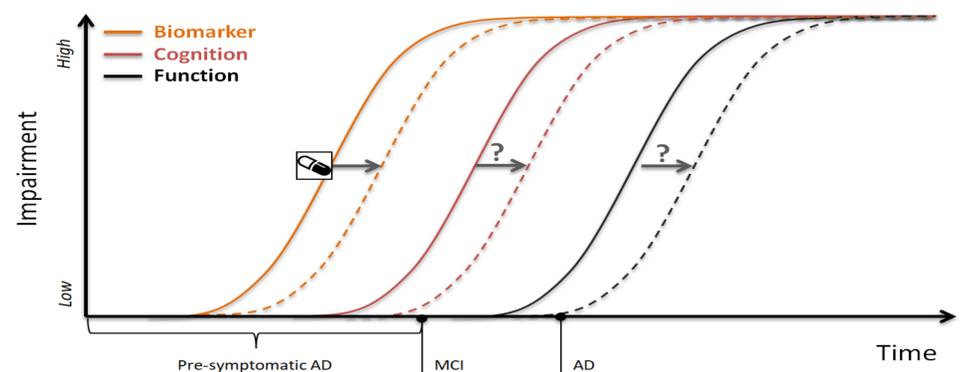

Figure 2. Evaluation of long-term effects of AD intervention applied at pre-symptomatic stages will have to be based on predictive modelling

5. How to weigh the ethical and social implications of pursuing the preventive approach in AD (e.g. turning otherwise healthy individuals into dementia patients) against. forsaking this therapeutic paradigm, given the large and prospectively growing burden of AD and a major public concern.

Conclusion

Predictive modelling will be an integral feature of the future preventive approaches to AD targeting pre-symptomatic "at-risk" individuals, reducing but not eliminating the uncertainty as to who will develop the disease, who is the best candidate for treatment and what is the overall value of this approach to society.

The discussion about the ethical issues and social implications associated with the use of predictive modelling for AD prevention needs to be complemented by a reflection on the consequences of forsaking this therapeutic paradigm since at the moment there seems to be no viable alternative that would alleviate the growing burden of AD.

References

1. Arias, J. J., & Karlawish, J. (2014). Confidentiality in preclinical Alzheimer disease studies When research and medical records meet. Neurology, 82(8), 725–729.
2. Fry, S. T. (1999). Ethical Issues in Alzheimer Disease Research. Alzheimer Disease and Associated Disorders, 13(Suppl. 1), S54–S58.
3. Gauthier, S., Leuzy, A., Racine, E., & Rosa-Neto, P. (2013). Diagnosis and management of Alzheimer's disease: Past, present and future ethical issues. Progress in Neurobiology, 102, 99–110.
4. Gauthier, S., Rosa-Neto, P., & Kass, J. S. (2016). Ethical considerations for the use of next-generation Alzheimer drugs in symptomatic and at-risk patients. CONTINUUM Lifelong Learning in Neurology, 22(2, Dementia), 615–618.
5. Gustavsson, A., Green, C., Jones, R. W., Förstl, H., Simsek, D., de Reydet de Vulpillieres, F., … Wimo, A. (2017). Current issues and future research priorities for health economic modelling across the full continuum of Alzheimer's disease. Alzheimer's & Dementia, 13(3), 312–321.
6. Hampel H, O'Bryant SE, Castrillo JI, Ritchie C, Rojkova K, Broich K, Benda N, Nisticò R, Frank RA, Dubois B, Escott-Price V, L. S. (2016). PRECISION MEDICINE - The Golden Gate for Detection, Treatment and Prevention of Alzheimer's Disease. The Journal of Prevention of Alzheimer's Disease, 3(4), 243–259.
7. Hsu, D. C., & Marshall, G. A. (2017). Primary and Secondary prevention Trials in Alzheimer Disease: Looking Back, Moving Froward. Current Alzheimer Research, 14(4), 426–440.
8. Illes, J., Rosen, A., Greicius, M., & Racine, E. (2007). Prospects for prediction: Ethics analysis of neuroimaging in Alzheimer's disease. Annals of the New York Academy of Sciences, 1097, 278–295.
9. Johnson, R. A., & Karlawish, J. (2015). A review of ethical issues in dementia. International Psychogeriatrics, 27(10), 1635–1647.
10. Karlawish, J. (2011). Addressing the ethical, policy, and social challenges of preclinical Alzheimer disease. Neurology, 77(15), 1487–1493.
11. *Khoury, M. J., McCabe, L. L., & McCabe, E. R. B. (2003). Population screening in the age of genomic medicine. The New England Journal of Medicine, 348(1), 50–58.
12. Paulsen, J. S., Nance, M., Kim, J. I., Carlozzi, N. E., Panegyres, P. K., Erwin, C., … Williams, J. K. (2013). A review of quality of life after predictive testing for and earlier identification of neurodegenerative diseases. Progress in Neurobiology, 110, 2–28.
13. Peters, K. R., Lynn Beattie, B., Feldman, H. H., & Illes, J. (2013). A conceptual framework and ethics analysis for prevention trials of alzheimer disease. Progress in Neurobiology, 110, 114–123.
14. Roberts, J. S., Dunn, L. B., & Rabinovici, G. D. (2013). Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues. Neurodegenerative Disease Management, 3(3), 219–229.
15. Sarazin, M., Chiappe, S. G., Kasprzyk, M., Mismetti, P., & Lasserre, A. (2013). A survey of French general practitioners and a qualitative study on their use and assessment of predictive clinical scores. International Journal of General Medicine, 6, 419–426.
16. Strech, D., Mertz, M., Knüppel, H., Neitzke, G., & Schmidhuber, M. (2013). The full spectrum of ethical issues in dementia care: Systematic qualitative review. British Journal of Psychiatry, 202(6), 400–406.
17. van der Vorm, A., Vernooij-Dassen, M. J. F. J., Kehoe, P. G., Olde Rikkert, M. G. M., van Leeuwen, E., & Dekkers, W. J. M. (2009). Ethical aspects of research into Alzheimer disease. A European Delphi Study focused on genetic and non-genetic research. Journal of Medical Ethics, 35(2), 140–144.
18. *Visser, P. J., & Tijms, B. (2017). BrainAmyloid Pathology and Cognitive Function. Alzheimer Disease Without Dementia? JAMA - Journal of the American Medical Association, 317(22), 2285–2287.
19. *Waljee, A. K., Higgins, P. D. R., & Singal, A. G. (2013). A Primer on Predictive Models. Clinical and Translational Gastroenterology, 4(12), e44-4.
20. *Wilson, J. M. G., & Jungner, G. (1968). Principles and Practice of Screening for Disease. Public Health Papers 34. Geneva: World Health Organization.
21. Wimo, A., Ballard, C., Brayne, C., Gauthier, S., Handels, R., Jones, R. W., … Kramberger, M. (2014). Health economic evaluation of treatments for Alzheimer's disease: impact of new diagnostic criteria. Journal of Internal Medicine, 275(3), 304–316.

* Reference not included in the targeted literature review.

www.roadmap-alzheimer.org