PLOS Science Wednesday: Hi Reddit, my name is Igor and I developed a prognostic model that predicts the progression of mild cognitive impairment to dementia due to Alzheimer's disease over a three-year period – Ask Me Anything!

PLOSScienceWednesday [1] and r/Science AMAs[1]

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REDDIT

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Hi Dr. Kolorev, very interesting article indeed. A few questions I have when reading it. They turned out to be quite long, sorry for that :P

1. More than half of the MCI patients progress to Alzheimer's within 3 years? That seems insanely high to me, while the criteria for being considered MCI do not seem very stringent and also quite subjective when reading the reference that is mentioned there. It's not quite clear for me how these people were recruited to the ADNI-1 study, but it does not seem unlikely to me that these people represent a more severe type of MCI impairment than the idea you get when reading the criteria for it. Obviously a prediction model does not need the same performance when 50% of the patients will develop the disease as when only 10% will do so. Do you think this might influence your results? Related to this part, how representative is the included MCI population for people with MCI in the general population?

2. How do you think the prediction model could be implemented in clinical practice? Regarding the fact that it uses an MRI scan and genotyping and proteomics, it sounds like it would be very very expensive to use in routine care for those with MCI, *especially* if the rate of progression from MCI to AD turns out to be lower in practice compared to what it was in this study. Or do you see this study more as a pointer for further study into how the factors you found can influence the progression from MCI to AD and what could be done about that?

3. If you say have a patient, you run him through the model and it turns out he has a very high chance of progression to AD, can anything be done nowadays to prevent or slow the progression, or would it purely be prognostic (which would probably also be hugely appreciated by patients I imagine)?

Thanks!

n23_

Thank you for your excellent questions!

1. The progression rate from mild cognitive impairment (MCI) to Alzheimer's disease (AD) varies with the type of MCI - that is people with amnestic MCI who have memory loss - develop AD at a greater rate than those who have non-amnestic MCI (where the predominant cognitive deficits are of the non-memory type, e.g. attention, language, visuospatial function, etc). In our study we analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which recruited people with amnestic MCI in a research setting and referred to a specialty memory disorder clinic. People with MCI in research-based settings, including memory clinics, tend to have a greater risk of progression (7-15% per year) as compared people with MCI living in the community (4-8% in some studies). Thus, the group of people recruited in the ADNI and other similar studies tends to be enriched with people at greater risk of developing AD. Thus, there is a limitation in generalizing the results from our study and other work based on ADNI data to the larger population. For various reasons described in our paper, we also did not include every person with MCI from the ADNI dataset in our analyses. Thus, the overall progression rate from MCI to AD cannot be estimated based on the data we used in the paper.

2. Our model for for predicting which MCI patients will progress to AD dementia was most accurate when using cognitive and functional assessments (i.e. paper-and-pencil tests) and a brain MRI scan. Although currently AD and MCI are both diagnosed clinically, based on a history and physical exam, both of these tests are generally already obtained by a neurologist or psychiatrist as part of the work-up of cognitive impairment. However, our model and similar published models still need to be validated and translated into clinical practice. They are not ready for prime time!

3. At this moment, the only FDA approved treatments for Alzheimer's disease are for symptomatic relief only. There are no approved treatments available that prevent or slow the progression of AD, but there are several ongoing clinical trials testing these new "disease-modifying" AD therapies. The use of the prognostic model would be to identify patients who are at greatest risk of progression to AD for participation in clinical trials. This type of prognostic tool is not quite ready for clinical practice yet. As far as informing patients and their families of the future risk of Alzheimer's disease, without the current availability of disease-modifying therapies, that's a highly controversial issue from an ethical standpoint. In some cases, knowing this information may help patients and their families plan for the future, but this issue must be considered on case-by-case basis.

What is the youngest person this technique has ever been used on?

I am 30, my mother is 60, her mother died of Alzheimer's at 90. Both myself and my mother have cognitive memory decline.

PennySun29

Thank you for your question, and I'm sorry to hear about your grandmother. Generally, research on the biomarkers of Alzheimer's disease (AD) has focused older adults who are 60-90 years old, as is the case of the Alzheimer's Disease Neuroimaging Initiative, which collected the data we used in our work. The most common form of AD, known as sporadic AD (as opposed to familial AD), occurs rarely prior to age 65, and its risk grows with increasing age. Thus, research studies attempting to identify biomarkers and develop new diagnostic methods have focused on this age group. However, there is a growing recognition that AD may begin a decade or more before the symptoms begin. Thus, there are increasing efforts to develop new diagnostic methods and to conduct preventative clinical trials in people who show no symptoms of cognitive decline but may be at risk for developing AD (e.g. genetic risk factors or based on early changes seen on brain scans or laboratory tests). This is a very exciting, rapidly developing but challenging area, and much work remains to be done on both the research and the clinical sides. One such clinical trial is the A4 study (http://a4study.org).

EEEExcellent work, Igor!

All seriousness though, 80% is an impressive statistic. Was there any sort of other previous tests/predictive diagnosis that was in use, and what was it's success rate? Also, how will the efficacy of diagnosis potentially affect treatment to slow/halt the progression of degeneration?

thebrandedman

Thank you for your comments/question.

Several research studies have used various methods, such as cognitive tests, brain imaging, and blood and cerebrospinal fluid biomarkers, to develop predictive approaches for identifying people at risk for developing dementia. No single test or biomarker has a very high predictive accuracy, and the best individual biomarkers tend to vary in accuracy from 60-70%. Other researchers have been able to attain prediction accuracies of 75-85%, depending on what biomarkers they analyzed, how long the time frame for prediction was, and the inclusion criteria for the participants in their study. Mild cognitive impairment (MCI) has been viewed as a transitional "at-risk" stage in clinical practice, but just using the diagnosis of MCI to predict the development of future dementia or AD is not a reliable approach. To my knowledge, no test for predicting progression to dementia has been widely used clinically. Accurate early diagnostic (or prognostic) approaches are critical in the fight against Alzheimer's disease (AD). The research community has shown convincing evidence that AD likely begins at least a decade (and likely longer) before the onset of symptoms. By the time a person with AD starts to show symptoms, there are significant, irreversible brain changes. Therapies for preventing and/or slowing down the degeneration caused by AD are likely to work best when initiated early in the disease course. Certainly, the tests must be accurate enough to identify with high accuracy people who will likely develop AD or dementia (so that they can be treated early). However, the tests must also not falsely identify healthy people as having AD or an increased risk of developing dementia. As most treatments, AD therapies may have side effects, and we should be treating only people at high risk for developing AD based on accurate prognostic / diagnostic tests.

Hi Dr. Korolev, could you speculate on why sex was not a strong predictor of progression from MCI to AD given a recent study by Lin et al. (doi: 10.1016/j.trci.2015.07.001), also using data from ADNI, which showed women tended to progress more quickly than men? Furthermore, approximately 2/3 of individuals with AD are women, so what are some factors that you think driving are the lack of effect in sex?

littlesnow

We did examine sex as one of more than 700 potential predictors of progression from MCI to AD. However, our analysis was not designed to identify every possible predictor of MCI-to-AD progression but rather to identify a small number of predictors that, when used together, maximized the accuracy of the prediction. The best performing model incorporated scores from cognitive/functional assessments and structural MRI measures and predicted progression with 80% accuracy. Although sex may have an effect on the rates of cognitive and functional decline, as suggested by Lin et al. (2015), our analyses did not identify sex as a unique predictor that added significant predictive information over and above the other included predictors. It's possible that the effects of sex are already in part reflected in the cognitive / functional assessments and brain MRI measures that were selected as predictors in our model (i.e. predictive information provided by sex may be redundant). Alternatively, it's possible that sex was not identified as a reliable predictor of progression in our study because we used a different dependent variable than Lin et al. Because we used a binary outcome variable (clinical diagnosis of progression or no progression from MCI to AD dementia), as opposed to a more fine-grained outcome variable such as scores on a specific cognitive or functional assessment (e.g. ADAS-Cog, CDR) as used by Lin et al., our approach may not have been sensitive enough to identify sex as

a predictor of progression.