

PLOS Science Wednesday: Hi reddit, I'm Ole Andreassen and my colleagues and I developed and validated a new genetic score to predict the age of Alzheimer's disease onset – Ask Me Anything!

PLOSScienceWednesday<sup>1</sup> and r/Science AMAs<sup>1</sup>

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April 17, 2023

### **Abstract**

Hi Reddit, My name is Ole Andreassen and I am a Professor in Psychiatry at University of Oslo. I have also a clinical position where I see patients regularly in the outpatient clinic at Oslo University Hospital. My research focuses on severe mental illness and neurodegenerative diseases. We recently published an article titled Genetic assessment of age-associated Alzheimer's disease risk: development and validation of a polygenic hazard score in PLOS Medicine. In this paper, we describe the development and validation of a new genetic score to predict Alzheimer's disease age of onset. Our results show that genetic data can be combined with epidemiological information on dementia incidence rates from the US population to derive a score that can predict age-specific risk for Alzheimer's disease. I'll be answering questions at 1pm ET – Ask Me Anything!

[REDDIT](#)

# PLOS Science Wednesday: Hi reddit, I'm Ole Andreassen and my colleagues and I developed and validated a new genetic score to predict the age of Alzheimer's disease onset -- Ask Me Anything!

PLOSSCIENCEWEDNESDAY [R/SCIENCE](#)

Hi Reddit,

My name is Ole Andreassen and I am a Professor in Psychiatry at University of Oslo. I have also a clinical position where I see patients regularly in the outpatient clinic at Oslo University Hospital. My research focuses on severe mental illness and neurodegenerative diseases.

We recently published an article titled [Genetic assessment of age-associated Alzheimer's disease risk: development and validation of a polygenic hazard score](#) in PLOS Medicine. In this paper, we describe the development and validation of a new genetic score to predict Alzheimer's disease age of onset. Our results show that genetic data can be combined with epidemiological information on dementia incidence rates from the US population to derive a score that can predict age-specific risk for Alzheimer's disease.

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How expensive might it be for an individual to get themselves tested using your method?

[Dr\\_Silk](#)

Author: Rahul Desikan All the SNPs we used in our paper are available on any high throughput commercial SNP-chip array (like Illumina) so getting these SNPs should be not expensive (likely <\$100). Once you have the SNPs, using our paper you can figure out your own PHS, in theory. We are working on formally offering this test through clinical practice.

How expensive might it be for an individual to get themselves tested using your method?

[Dr\\_Silk](#)

The method is not available for routine testing yet, but the method is based on relatively inexpensive genotyping technology. Thus it will be possible to make it into a routine assessment - but some work is needed before this is possible.

Having lost my father just over 2 years ago to Alzheimer's, I thank you for your work. In the same vein I am absolutely terrified of what your findings could mean for me. What is your end goal with early detection? Do you feel that advance warning will lead to more proactive behaviors or resigned depression, given that no proven cure has yet to be discovered?

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[turbinepilot76](#)

Author: Rahul Desikan With our new polygenic hazard score (PHS), our hope for early detection is to use this test to help identify non-demented older folks who are at high risk for AD dementia. Although you cannot predict how any single individual will react to knowing their personal risk for a fatal neurodegenerative disease, as a practicing clinician, I have found that better understanding your risk for a disease like AD can help patients plan for the future and focus on quality of life issues

Have you had accidental discoveries during your research?

[Scarbane](#)

yes, plenty of discoveries that we did not anticipate. This is what makes science so exciting.

What should people do with this info? From (what little) I know, the preventive and therapeutic options are extremely limited. Personally, my first thought would be to splurge on more travel (rather than retirement savings and figure out a good assisted suicide plan.

[balmergrl](#)

Author: Rahul Desikan As I mentioned above, it's really a personal decision what you do knowing your genetic risk.

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[balmergrl](#)

As we mentioned elsewhere, this decision is extremely personal

Good morning, and interesting work! When the genetic assessment for breast cancer risk arose for BRCA1 and BRCA2 as predictive markers, certain people felt there was an ethical risk associated with people finding out they are at a greater risk for developing breast cancer, as they may take unnecessary proactive measures (e.g., double mastectomy). Do you foresee any pushback from the scientific community in a manner similar to this for prediction such as early onset Alzheimer's, etc.? If so, how do we deal with the ideal ethical obligations of predictive risk for Alzheimer's onset? Thanks!

[cardsfan24](#)

Author: Rahul Desikan This is a really good question. I think the analogy to BRCA1/2 is applicable to our score because our PHS is not a diagnostic test; that is, if you have BRCA1/2, you will get breast cancer. However, if you have a high PHS, it means that you are at high risk for AD but does not guarantee you will get the disease (subtle difference). As such, our test is more analogous to a 'risk factor' like atherosclerosis is to heart disease. As several people have pointed out, we don't know yet if there are things you can modify (lifestyle, envt variables, develop more cognitive reserve, etc) that can delay your onset even if you have a high genetic risk for AD

It is my understanding of Alzheimer's is that it has a strong environmental component. Especially diet

seems to play a role with some research even going so far as calling the disease preventable on a plant based diet. This is supported by age corrected epidemiology of groups in the Third World and groups on non-standard diets in the developed world. My question then:

This genetic predictor of age of onset, is it or could it be linked to additional environmental predictors to come to a complete picture? And if not, how useful is this predictor for groups who eat healthier than standard diets such as vegetarians, those on plant based diets (upwards of 95% plant based) and vegans?

[AlwaysUnite](#)

Author: Rahul desikan Great question and the answer is we don't know. Great paper in NEJM earlier this year showing that even among people with high polygenic risk, a favorable lifestyle resulted in good coronary heart disease outcome:

<https://www.ncbi.nlm.nih.gov/pubmed/27959714>

we are now exploring whether something similar occurs with AD

It is my understanding of Alzheimer's is that it has a strong environmental component. Especially diet seems to play a role with some research even going so far as calling the disease preventable on a plant based diet. This is supported by age corrected epidemiology of groups in the Third World and groups on non-standard diets in the developed world. My question then:

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[AlwaysUnite](#)

This is a good point. The genetic risk we have observed (risk for a certain age of onset), is based on the average in the given group. There could be environmental factors that reduce or increase the risk from the genes within this group. However, we did not investigate these environmental factors in the present study - it would be very interesting. But the type of diet which can affect disease onset is outside of my expertise, sorry.

Are you ever mistaken for Ole Anderson, professional wrestler?

[TheVicSageQuestion](#)

never

What is the quantity predicted by the model? A probability distribution per year?

[Glxbt76](#)

Author: Rahul Desikan For any given individual, knowing your age and genotype information, we can tell your annualized risk (cumulative incidence rate) for AD; that is, if you haven't already developed AD, what is your age-associated risk for any given year?

Would factors such as having a brain injury or substance taking be taken into account?

[EmperorKira](#)

This will be the next step for the model. We are working to include other factors into the model, like brain imaging and clinical variables. It would be really helpful to also include environmental factors in the prediction model. This is technically possible, but first we need to be sure we have the correct size of the risk from these environmental factors for Alzheimer's disease.

How hopeful are you that a cure or highly effective treatment method will be developed in the next decade? Is it really likely?

Secondly, does 'brain exercise (using it more actively by learning, solving puzzles, etc. You know) really help?

[iamnottheuser](#)

Author: Rahul Desikan Really depends on what you mean by a 'cure' -- even among those people with very low genetic risk, we found that they eventually develop AD. That is, if you live long enough, you will get AD (just like osteoarthritis). As such, a 'cure' may mean therapies that can delay age of onset.

How hopeful are you that a cure or highly effective treatment method will be developed in the next decade? Is it really likely?

Secondly, does 'brain exercise (using it more actively by learning, solving puzzles, etc. You know) really help?

[iamnottheuser](#)

I am optimistic about developing more efficient treatment of Alzheimers the next decade - a lot of resources and new compounds are currently being tested. The problem in recent trials has been that many drugs have been initiated too late in the disease process, and then it seems to be too late. Many recent trials have failed.

Brain exercise doesn't hurt, it keeps you active and often makes you more social, but I am not aware of any study specifically showing delay of dementia.

What is the time-frame for this score to start getting used?

[ilrasso](#)

We need to work more on validating the score in different ethnic groups, and perform rigorous testing before it can be used in clinical setting. Hard to guess, but 3-5 years?

### **Patient Expiration Date**

Information bias is Cognitive bias - it causes healthcare providers to order tests that produce information providers do not realistically expect or intend to use for the purpose of making a medical decision. Said in another way, medical tests are indicated when the information they produce will be used to generate a net benefit for an individual patient.

For example, there is a big debate currently raging between the USPSTF and Urologists on whether or not to use PSA testing to screen for Prostate Cancer in men. The United States Preventive Services Task Force [[USPSTF, 2012](#)] does not recommend PSA screening for prostate cancer, noting that the test may result in "overdiagnosis" and "overtreatment" because "most prostate cancer is asymptomatic for life" and treatments involve risks of complications including impotence (erectile dysfunction) and incontinence. **The USPSTF concludes "the potential benefit does not outweigh the expected harms."**

Alzheimer's Disease (AD) currently has no FDA approved cure or proven standard of care to reverse the disease. In developing a genetic protocol to predict the age of AD onset, no doubt a question has arisen within your medical research team about the dilemma of balancing the benefits and harms of informing patients they will develop a debilitating disease at a certain age for which there is no cure.

So how did your team answer this question? Does the individual derive any net benefit from this new protocol? How about the medical community at large in terms of generating data for new insights in possible future treatment?

[Zfriske](#)

This is really valid point that we have though a lot about. The most obvious application of the test for short term benefit is to use it in clinical trials to stratify the study sample - i.e. select patients with same genetic risk in treatment and placebo group, so the effect of the drug becomes clearer (less confounded by variation in the sample)

Hello Dr. Andreassen!

I am an intern with a group called Covenant Alzheimer's. We offer a range of services from support groups to free GPS bracelets for those with cognitive impairments prone to wandering, to education programs, free memory screenings, and even free home safety checks. I am currently building an education/support group hybrid for elementary-middle school aged children coping with family members with Alzheimer's or dementia.

If someone tests positively for early onset (or even any onset at all), do you have a plan to set up some sort of support or education program for patients and families? I know the caregiver is really the person dealing with the brunt of the stress in these situations, especially with the unique facet of grieving the loss of a loved one before they are gone.

I've been surprised to see that programs like ours are not commonplace - it seems as if dementia and Alzheimer's are a price we pay for sustaining longer life, but we are still trying to figure out a way to cope.

Thank you for all the work you do!

[kittykatie0629](#)

Thanks for your comments. As mentioned, we have focused on developing the method. The implementation and follow up of the method has just started, and here we need collaboration with patients, families and support groups.

Ummm, when will it be publicly available

-Sorry if its already been asked

[Azazels Azure](#)

Author: Rahul desikan As we speak, we are working on making this more broadly available. However there are still a few more things to do, please check:

<http://journals.plos.org/plosmedicine/article/comment?id=10.1371/annotation/3472f94d-a39b-4ab1-aa15-550a8935934e>

I literally read this last week and really enjoyed it.

We're planning to apply it to other phenotypes, not necessarily dementia, but related.

I'm interested: you looked at 1,854 SNPs - firstly were these all independent, and secondly was there any evidence that the benefit of adding more and more SNPs tailed off? Sort of like with PGR scores where you can tally SNPs associated at  $P < 0.001$ , or  $P < 0.01$ , or  $P < 0.05$ , but a lot of the time it's diminished returns in terms of what you gain from more SNPs?

Basically, could your paper have done exactly the same looking at even 100 SNPs, stratified by APOE genotype? Escott-Price et al looked at far fewer SNPs and found similar results:

<http://www.dementiasplatform.uk/wp-content/uploads/2015/12/Common-polygenic-variation-enhances-risk-prediction-for-Alzheimers-disease.pdf>

I love your paper, anyway: sort of thing I aspire to! Great you're doing this. I hope you'll be at BGA in June.

[dl064](#)

Author: Rahul desikan Big difference between our paper and the Escott-Price PGS Brain pape is that we don't assume that Alzheimer's is a dichotomous process where some folks get diseases (cases) and others don't (controls). Given the age dependency, if you live long enough, you will get AD. In this framework, you have to use a survival model where you look at EVERYONE'S risk for getting AD -- not just cases

I've seen in pictures that people with alzheimers get brain atrophy, and they can remember old memories better than new ones. Why doesn't the old memories disappear as much as the new ones? Does the brain atrophy affect different parts of the brain in different rates?

[Hmolds](#)

Author: Rahul desikan Old memories are 'stored' in all parts of your cerebral cortex but the ability to make new memories is done by the entorhinal cortex and hippocampus, which are the two earliest regions affected in AD

Hi, thanks for doing this AMA. I'm here not as someone overly interested in Alzheimer's specifically, but rather someone interested in slandering sugar as much as possible.

That said, there is a [study](#) I've read essentially describing Alzheimer's as Type 3 Diabetes. Therefore, it seems to have a strong environmental component - can you explain how your genetic market and this environmental component interact? I would greatly appreciate an answer, all the best.

[chrysocollus](#)

We have not tested interaction. We can easily do this if we had the information available, but this was missing for many of the participants in the study. I agree with you that if we knew what environmental

factors were interacting, it could be easier to intervene and modify the risk.

Are there any plans to make this test cross-referable with other genetic testing agencies? For example, will I be able to take my raw 23andme data and download it to your system to give me an Alzheimer's score?

[FitDontQuit](#)

Author: Rahul desikan Our hope is to indeed raw output from vendors (like 23andme) to calculate PHS

With the current speed at which medical science is progressing, how long do you think it will take before a cure of any kind appears for Alzheimer's?

[Sorrowwood](#)

I think it is possible within 10 years, but this is very speculative.

Can you give us a very concise rundown of the most significant predictive factors?

[ACoconutAnt](#)

We have listed the genet variants that were included in the model in the paper at PLOS Medicine, Desikan et al.

Will this be available for public use, assuming one already has genetic information available from companies like 23andme, and FTDNA?

[itspotatoman](#)

not yet - the implementation of such tests will need rigorous evaluation. But the genetic information available from i.e. 23andMe would be sufficient to do the scoring.