As usual, we could get to only a fraction of your questions. We hope this was helpful, and thanks very much for joining us.

Hi everyone, and welcome to our live chat on Alzheimer’s disease. We scheduled it for right after the Alzheimer’s Association International Conference, and will be referring to that from time to time (as AAIC, or our fingers will fall off from all the typing). Let the questioning begin.

Is there anything new regarding possible association between aluminum and AD?

That has been basically discounted. If only eliminating risk were that easy.

Considering the novel approaches being proposed in light of our learnings from past clinical efforts, are there key derisking readouts that would be meaningful to consider before a large scale (and time intensive) clinical trials are considered?

Really, the main thing I want to see on the amyloid front is results from a study in people with extremely high genetic risk. On the earlier stage work, everything is interesting and nothing was definitive.

Another pipeline analysis released at AAIC this week...similar to Cleveland Clinic’s but with slight differences... https://www.usagainstalzheimers.org/press/new-analysis-provides-
Adam Rosenberg's STAT piece "The trouble with mice as behavioral models for Alzheimer's and other neurologic diseases" (April 16) prompts me to ask what can be expected in developing more informative and reliable mouse models for AD and other dementias?

I don't really know but this is such a great question!

I do hope that looking at specific mutation will give us both better animal and culture models. I also think the increasing ability to work with organoids and human tissue could be a big plus. So that would be where I'm optimistic.

What if anything appears to be promising? Can the FDA speed up approvals, or trial drugs?

I don't think the FDA is the bottleneck at all, and the agency has already signaled it will be "flexible" when it comes to these drugs. If a drug is effective, there shouldn't be much doubt. But knowing that requires running clinical trials that take a lot of time and a lot of money. That's just a difficult reality.

Re: Christina S comment about data sharing, this is an extremely important area in terms of advancing the entire field. Representative efforts include AMP-AD and GAIIN.org. At AAIC 2019 the research community confirmed its commitment to tackling this disease collectively.
There are a few studies on the therapeutic potential of ketone bodies as a therapeutic for AD. Anything new in this area? What's your sense of its acceptance (or level of interest/excitement around it) as a potential therapeutic for AD within the field?

I think this is going to face a lot of skepticism, but history also says people are willing to try a lot of things. I hope this doesn't lead to people putting Alzheimer's patients on keto diets, though. I think that could be cruel. I remember by grandfather really liked his ice cream.

How much difference would less invasive AD diagnostics (blood vs scan) make to clinical trial recruitment or the pace of drug development? Is more accurate/faster/easier diagnosis of AD a "top 3" bottleneck to therapy development or not?

I think it is a major bottleneck. There was a fascinating study that came out of AAIC of blood tests that might make it easier to identify patients who have Alzheimer's. That's would be start. I think we need three things if we're ever going to develop an Alzheimer's drug: (1) a valid mechanism (2) a way to identify patients (3) a biomarker that shows whether we are engaging the mechanism. It’s a pretty high bar.

Any thoughts on the relationship between diabetes and Alzheimer's disease? Any new information or recent learnings that might make a big impact on preventing or treating AD?

Diabetes is a well-recognized risk factor. Maybe because it harms the brain independently, lowering cognitive reserve. Maybe because it increases inflammation. Lots more here, for instance.

All clinical trials to date have enrolled symptomatic patients with AD or mild cognitive impairment. Given that AD pathology begins decades before clinical symptoms, comment on the prospects for an anti-beta-amyloid vaccine as a true preventative therapy rather than a
disease-modifying therapy.

Jul 18, 2019 11:37 AM

The A4 trial of solanezumab was in the prodromal stage. The recent trial of Biogen’s aducanumab was pretty early, too. The question, again and again, is how early are we going to give these drugs? At some point it’s not realistic.

Jul 18, 2019 11:30 AM    B Fallon

Is anyone using the RWD databases of prescription histories to look for associations between existing drugs and incidence of AD to data mine for effects of existing drugs on disease frequency? Wasn’t metformin being suggested as a possible help? Would the VA or NHS in UK or Japan have useful data?

Jul 18, 2019 11:37 AM

It's very tough to use RWE for efficacy data, and I think most of the efforts now are for testing current or expected uses or comparing the safety of drugs, where RWE is well-established.

After the experience Pfizer just had with using claims data to study Enbrel, I think companies may be more gunshy about this, because there will be positive results you don't believe.

One of my big rules for evaluating drug studies is: "Will the sponsor do anything different depending on the result?" What would an RWE study have to look like to lead to running a randomized clinical trial with that drug?
We would like to see attention given to the work of Dr. Dale Bredesen. His approach to treat cognitive decline identifies all of the potential contributors and addresses them for best outcome. Why blind treatment remains the standard of care and what causes Alzheimer's is under-reported.

Fair enough. He lays out his approach in a recent book, 'The End of Alzheimer's.' It is, as you imply, multi-factorial (diet, supplements, sleep, much more). He couldn't get support for a clinical trial because no one will back a study with so many variables--the conventional wisdom is, mostly, one at a time. Which, as others in the audience have pointed out, may never work for Alzheimer's.

Thoughts on needing to address the disease through multiple mechanisms at once (tau entanglement + b-amyloid) to see an effect size in patients who may be showing symptoms of AD? Given the problem this disease poses, would FDA be comfortable with testing multiple unapproved API's at once?

There has been experience testing drugs that only work in combination before going back forever. I mean, clavulanate potassium has no single-agent activity against bacteria. But the FDA has certainly embraced this in cancer. BRAF inhibitors only work in colorectal cancer with other drugs, for instance.

There would probably have to be some single-agent efficacy studies, but I don't think it's going to be that difficult in the current era of "flexibility." I really can't see the FDA standing in the way of anything promising here.

@ Michael S: One of the pharma companies did a poll about how many people still believe that amyloid is a worthy target at it's sponsored symposium. I believe the response was something like 80%!

Thanks, Christa!
Would be interested in the right to try law and what trials would be helpful for moderate+ ad. Patients. Trials seem to be very limited for patients in the range of moderate +.

Sharon did a great story last year on how very little there is in the pipeline. [https://www.statnews.com/2018/08/10/alzheimers-pipeline-clinical-trials/](https://www.statnews.com/2018/08/10/alzheimers-pipeline-clinical-trials/)

This is an area where I’d be very worried about people who want the right to try experimental drugs. We know the failure rates are astronomical. I think it’s worth trying treatments that have made it that far, but, honestly, most hope here is going to be false. That’s terrible, but it is the reality we are looking at.

Do you have any thoughts on what magnitude of treatment effect will be required for it to be considered clinically significant?

Reasonable people can differ, especially about whether cognitive tests or activities of daily living matter more. But the field seems to be converging on 3 points on ADAS-cog, as per [this paper](https://www.statnews.com/2018/08/10/alzheimers-pipeline-clinical-trials/).

Is there any hope for the beta-amyloid theory? Are there any companies developing therapies with this approach that give some glimmer of hope?

The genetics still make some sense, and it definitely plays a role. But given all the failures, I don’t see much hope. But I’ve been wrong before! Frequently! The study I would watch is Roche’s study of crenezumab in patients who carry the PSEN1 mutation. If an amyloid drug can’t prevent the disease in patients who are certain to get it, well....
Matt, in your "Celebrated Drug Hunter" piece you mention that Biogen was punished on Wall Street after its announcement, losing $200 billion in market cap. Given this risk, how can the burden of discovery and new pathways to commercialization be shared, beyond NIH funding alone?

One of the problems here is that investors still assign a lot of value to these programs, despite the dismal odds. On the bright side, that allows companies to raise money before losing it. We've certainly seen companies partnering with each other in response to this, going back to the JNJ-PFE-ELN partnership to the Biogen-Eisai partnership to the Novartis-Amgen one.

If the risk of failure is 100%, it doesn't really matter how you manage it, does it?

I tend to think we should be spending more money on basic research and less on late-stage studies until we have a real reason to believe something will work. Perhaps industry has been setting the bar for doing a large study far too low,

Elaine L.

Is there any indication in any research of whether the possible viral culprits are only simplex 1 or HPV? And further, concerning those who have been treated with anti-virals and show less incidence of dementia...was there a drug breakdown, i.e. zovirax, famvir or ??

So far, the strongest evidence links HSV to Alzheimer's. As for the drugs that seem to reduce risk, the key study found risk reduction with acyclovir, famciclovir, ganciclovir, valciclovir, and valganciclovir. Some had a stronger effect than others; see Table 6 in the above (open access) paper.
Is there a rough estimate what percentage of KOLs still support the beta-amyloid theory?

I'd love to see a survey on this... including trend lines from, say, 1990. With dates of failures of solanezumab, crenezumab, aducanumab, verubecestat... and all the other sad examples, marked. But no, I've never seen one. AAIC should have done a poll at its plenary sessions!

Any updates on NIH run DIAN studies? Any new revelations on the biomarkers that can indicate disease progression?

There were a bunch of DIAN papers at AAIC, but no blockbusters. You can follow its progress [here].

Research results you reported today indicate "adequate exercise" is one lifestyle factor that can help reduce incidence of dementia. How did the researchers define "adequate exercise"?

The AAIC study used 150 minutes or more per week of "moderate/vigorous leisure physical activity." So, half an hour 5 days per week (you get the weekend off!). Moderate-vigorous means walking at 3 mph or anything more strenuous. The 'leisure' part means it doesn't have to be a gym workout. Walk to work, break a sweat doing housework or yardwork, and you'll hit the mark.

Given the number of failed trials, is there any incentive for pharma to make the trial samples/data available for secondary use and/or combine all of the failed amyloid trial data together for data mining?
There’s certainly some, but this has been a slow process. There was some really interesting movement on this idea a few years ago, when first Medtronic and then J&J created a process working with Yale University’s Harlan Krumholz to make data from trials available to outside researchers. But I haven’t seen many companies take up that model. I don’t think we’re going to ever live in a world where pharma’s show proprietary data to just anybody. There will need to be a gatekeeper.

It also may be that a lot of the biomarker data we would really want will not be in the earlier trials! For instance, neurofilament light, or NFL, is a new biomarker entirely and looks like it might be useful! So it depends what samples have been saved.

Was there any response from the Alzheimer’s scientists that were criticized in the STAT “cabal” article? If so, was it to double down on their views or to apologize for doing bad science?

As you probably saw, I included responses from Drs. Paul Aisen of USC and Dennis Selkoe of Harvard, two leading long-term proponents of the amyloid hypothesis. Aisen said he “would reject the idea that we would have been further along if there had been more openness to other ideas.” Selkoe was more open to that possibility, though I would not characterize his response as apologetic. He said, “society has the right to ask, why haven’t we made more progress? I have no doubt that if we had done broader research we would be more advanced now. . . . I don’t think there was a purposeful attempt to scuttle other approaches.”
The beta amyloid hypothesis focused on what was 'erroneously described as 'early onset' Dementia/Alzheimer's. Now that AI can measure some of those previous pre-clinical manifestations, how can we re-focus research to before the disease is triggered -- since we don't know how to fix it post-trigger?

Let me refer back to the answer about the A4 trial. But again, this is tricky: 'preclinical' is another word for, 'the person does not have this disease.' No one has any idea whether giving an anti-amyloid antibody or anything else will prevent MCI or Alzheimer's, but the A4 trial should provide hints.

Some people think that there have been so many failures in trials because of the underlying heterogeneity of the disease. Has there been any progress towards identifying subtypes or other diseases mis-classified as AD that could be targeted more specifically?

A very important point. Yes, in early trials of amyloid-targeting drugs, some participants didn't even have amyloid deposits, so that was definitely a failure of patient stratification/use of exclusion criteria. But ID'ing subtypes of Alzheimer's is an active area of research. See this and this, for starters.

In light of your recent article regarding the a/d cabal. It would be most helpful to update us on Dr. Raymond Tesi (xpro 1595), Dr. Daniel Alkon (Neurotrope Bryostatin), Dr. Davangere Devanand (anti viral therapies). It seems to defeat the amyloid cabal.

We are definitely watching these as well as other clinical trials. Devanand told me he won’t have data for three years, but Neurotrope expects its next readout by late this year or early next. Fingers crossed.
@Edward T.: you seem to be in the field, so maybe you know more than me, but I thought this was a thorough debunking of the Post story: https://blogs.sciencemag.org/pipeline/archives/2019/06/06/a-missed-alzheimers-opportunity-not-so-much See also John Carroll at Endpoints.

Jul 18, 2019 11:19 AM

I agree very much with Derek's take here.

As noted before, I think if someone did believe this they would create a new TNF antibody to test it.

Jul 18, 2019 11:17 AM  Ted W.

Plausibility of the proposed link between tooth decay bacteria and AD

Jul 18, 2019 11:18 AM

You're referring to studies such as this from Sweden, and others that have found an association between periodontitis and AD. Gum disease causes systemic inflammation, and inflammation has risen up the list of suspects (as well as a drug target) for AD, so there's that. The strongest study came out in January: it went beyond mere association, finding toxic proteases ("gingipains") from the bacterium in the brains of Alzheimer's patients, and reporting that infecting mice with P. gingivalis increased production of Aβ (other scientists have found the same amyloid response in mouse brains to other microbes); and that gingipains were neurotoxic. The researchers then made small-molecule inhibitors of gingipains: in mice, the molecules reduced the bacterial load, blocked Aβ production, reduced neuroinflammation, and rescued neurons in the hippocampus. As per answer above, Phase 2 clinical trial of this approach is underway, sponsored by Cortexyme.

Jul 18, 2019 11:07 AM  Rohit V.

Any thoughts/comments on Alector's approach?

Jul 18, 2019 11:17 AM

It's certainly interesting to have a company out there, run by a veteran drug developer, that is so adamant about an alternative to the beta amyloid theory.

I recently spoke with Arnon Rosenthal, the CEO of Alector, and he argued that
the whole idea of targeting misfolded proteins -- not just amyloid and tau but alpha synuclein, also, is wrong. He argues that the brain's innate immune system fails and that this causes the disease, and that these proteins are a downstream result. It's like the city government failed, and we're trying to fix the lack of police officers by cleaning up the garbage.

I think this mirrors what a lot of us want to hear given the complete lack of progress in the amyloid space. And that would be my main concern: this is what we want to hear, and so it would be nice to believe, and you should always be skeptical of a just-so story.

On the other hand, using genetic data to validate targets makes sense. I thought the frontotemporal data was promising for what it was and am excited to see what they come up with.

Worth noting that Denali seems to be working in some of the same spaces.

Jul 18, 2019 11:15 AM  Niranjan B.

Are there reasons to be optimistic about the current mid to late stage pipeline? and what is thought to be the next promising candidate?

Jul 18, 2019 11:16 AM

Where to begin. Every year, a Cleveland Clinic team analyzes the AD pipeline; they released their latest on July 10. (Paper: [https://www.trci.alzdem.com/article/S2352-8737(19)30029-0/fulltext](https://www.trci.alzdem.com/article/S2352-8737(19)30029-0/fulltext)) Short version: the number and variety of agents has grown, so now we have anti-tau, neuroprotective, anti-inflammatory, regenerative (stem cells) and metabolic interventions, as well as anti-amyloid agents.

Drilling down, at AAIC yesterday (Wednesday), one study reported results with inhaled insulin, but the study had some strange complications. The first 49 participants (they had mild cognitive impairment or Alzheimer's) used what we'll call intranasal device #1. But it didn't deliver reliable amounts of insulin, so the next 240 people used device #2. After 12 months, the device #2 people had no cognitive benefits compared to a placebo group. But the device #1 people showed a trend for better cognition! Weird.

And in the open-label extension of the study, the device #1 people again had better scores on ADASCog-12 (a standard cognition measure) at months 15 and 18, vs. placebo. But the device #2 people--those with reliable insulin hits--still showed no cognitive benefit vs. placebo. Still, this is what the lead researcher said in a statement: “At 18 months, the results show a prolonged,
statistically significant benefit for the insulin-treated group who used the Device 1 that strengthens over time, with a pattern consistent with a disease modifying effect.”

FWIW, the Device #1 group showed a reduction in the amount of amyloid beta, the kind that forms amyloid plaques.

For you fans of the infectious-agent hypothesis, a 48-week Phase 2/3 trial of a drug targeting proteins released in the brain by P. gingivalis, bacteria that cause gum disease, began in April. Top-line results are expected in 2021.

Also, Neurotrope Inc. announced on Monday that it had finished collecting data in its Phase 2 placebo controlled clinical trial of Bryostatin-1, a weird compound that seems to reduce inflammation, hit amyloid, restore synapses, keep neurons from dying, and prevent the hyperphosphorylation of tau (which turns that peptide into neurotoxic tangles)—so pick your favorite AD explanation, and this drug (supposedly) fixes it. We’ll see.

What is the role of consumer genomics in prevention of Alzheimer’s?

Several direct-to-consumer genetics companies, including 23andme and MyHeritage, will tell you your ApoE status (the ApoE4 allele increases the risk of Alzheimer’s); Ancestry doesn’t give you a direct readout, but you can upload the data it returns to Promethease. ‘Prevention’ is a strong word, but there’s evidence you can reduce your risk of AD even if you have the higher-risk allele, according to a study that was presented at AAIC19: in people with ApoE4 and/or other genetic risk factors, scientists in England reported, people with a high genetic risk + healthy habits (no smoking, physically active, healthy diet) had a 32% lower risk of dementia than those with equal genetic risk but unhealthy habits. So, if you learn your genetic risk, you might be more motivated to adopt healthy habits.

It’s important to recognize the value of lifestyle interventions which are currently being tested in the US POINTER Study and other similar studies. Or the possibility of lifestyle plus pharmaceutical interventions as we currently do in hearth disease.
Very true. Unfortunately, every lifestyle intervention for Alzheimer’s has to do with prevention. I hope we’re not ready to give up on helping people who have already developed the disease.

Jul 18, 2019 11:12 AM    William B.

On April 1st the NIH announced that "The infectious etiology of Alzheimer’s" was now a high priority research topic. How much interest do you think there will be among existed Alzheimer’s researchers to apply for these grants. https://grants.nih.gov/grants/guide/notice-files/NOT-AG-19-012.html

Jul 18, 2019 11:13 AM

NIH is offering money. There is no universe in which there will be less demand than supply. If you're asking whether diehard amyloid scientists will apply, I can't wait to see. But there's no question scientists who have been studying other explanations of AD will apply.

Jul 18, 2019 11:11 AM    Edward T.

Why has no one challenged Amgen for their failure to investigate Enbrel for Alzheimer’s? Particularly in view of Richard Chou’s 2016 article showing Enbrel reduced Alzheimer’s in patients with RA, our work with perispinal Enbrel, and the Washington Post showing Pfizer deliberately buried their data?

Jul 18, 2019 11:12 AM

On the Pfizer study, I don’t think there was a credible case presented that they had a strong signal here. Certainly, if anti-TNF drugs show promise in Alzheimer’s, I’d expect a drug company to be interested. Given that Enbrel and Humira are both approaching the end of their patent lives, I would expect the tractable approach would be to develop a new anti-TNF antibody for this purpose. I’d love to see more data -- you reference some work I’m not familiar with -- but so far I’m not sure that this amounts to anything close to a slam dunk when we’re in an area with a 100% failure rate. As with most of Alzheimer’s, my question would be how you can get to proof of concept quickly.

Jul 18, 2019 11:03 AM    David Lowe

is there any ongoing or about to start discussions at government level eg NIH about the issues Sharon has raised
Jul 18, 2019 11:07 AM  Not that we've heard. OTOH, with the infusion of additional $$, NIH/NIA is supporting (finally) many more approaches to Alzheimer's, notably the infectious agent hypothesis. If only this were 10 years ago.

Jul 18, 2019 11:00 AM  Misha A.

Given that: a) definitive diagnosis of Alzheimer's is still possible only at autopsy; and b) an effective disease-modifying therapy for Alzheimer's is going to work best in presymptomatic or perhaps prodromal patients, how do drug developers stratify clinical trial participants?

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Jul 18, 2019 11:04 AM  This is the $100 billion question. If a disease modifying therapy can only work as a preventative, how do you identify the right patients ahead of time? How do you test it? I'm highlighting this because it's the right question. I don't think anyone has a good answer. If Alzheimer's weren't such a big problem, I can't see why anyone would dare attack this problem at all. It's only the size of the threat that makes it even worth trying.

Jul 18, 2019 10:49 AM  John F.

Any thoughts on a subsegment of the amyloid theory that suggests the issue may be toxic oligomers of beta-amyloid, rather than plaques which form later?

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Jul 18, 2019 11:00 AM  Misha A.

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Jul 18, 2019 11:03 AM  This was one of the first fallbacks for the amyloid camp after Elan's vaccine and then various mabs that did an okay/good job of removing amyloid failed to help patients. Go earlier!, they said--where earlier meant, soluble oligomers. A bunch of companies are developing molecules that mop up the oligomers or stop their formation--e.g. Alzheon (which explains its approach here), and Cognition Therapeutics.

Jul 18, 2019 10:49 AM  Christopher S.

Thoughts on new assays to detect AD earlier so therapeutics can be tested earlier in the course of disease -- where are we in terms of the development and validation of them.

Jul 18, 2019 11:02 AM  Given that: a) definitive diagnosis of Alzheimer's is still possible only at autopsy; and b) an effective disease-modifying therapy for Alzheimer's is going to work best in presymptomatic or perhaps prodromal patients, how do drug developers stratify clinical trial participants?
There is a ton of work in this area and it was a big deal at AAIC. We have cognitive tests, of course, and amyloid PET imaging. But cog/psych tests aren't perfect (or specific to Alzheimer's), and a not-insignificant percentage of people with amyloid deposits never show symptoms of Alzheimer's.

At AAIC, there were presentations on a bunch of new possibilities, but let me mention two, both blood tests (you can find the full story here).

One, developed by Dr. Akinori Nakamura of the National Center for Geriatrics and Gerontology in Obu, Japan, measures abnormal versions of amyloid-beta. In validation testing, it correctly identified 92% of people who had Alzheimer's and correctly ruled out 85% who did not have it, for an overall accuracy of 88%.

Another measures a protein called neurofilament light, a marker of axonal damage (damaged axons = damaged/destroyed synapses). NfL was high in people with Alzheimer's, other dementias, Parkinson's, depression, multiple sclerosis, and Lou Gehrig's disease — but unfortunately it can't tell who has which. Still, just 2% of cognitively-healthy people had levels above a threshold considered pathological; it's always good to have a low rate of false positives.

Just to make this even harder, there seem to be sex differences. A Canadian group reported at AAIC that, in women, biomarkers like amyloid-beta in cerebrospinal fluid didn't improve the accuracy of predictions about who would develop Alzheimer's beyond what cog/psych tests indicated. But in men, neuropsychological measures were not significant predictors, but CSF biomarkers of tau and Aβ were. Go figure.

What kind of contributions to this research do you expect to come from crowd-sourced genomics via companies like 23&me?

I don't really think that we can expect that much from the consumer genomics space here. 23andMe has had a fairly big impact in Parkinson's because it's an area with clear genetics and a very motivated patient population. I don't think SNP genotyping is going to give us a lot of information about what causes Alzheimer's, or lead to new drugs or diagnostics. It's just a less tractable problem.
Why isn’t Alzheimer’s approached as an autoimmune disease?

Jul 18, 2019 10:48 AM

It’s not so much viewed as an autoimmune disease as one in which the brain’s immune system doesn’t function properly. That is a major area of investigation for companies like Alector and Denali, both of which are looking at, among others, a target called TREM2, is thought to allow immune cells in the brain, called microglia, to detect pathologies.

What are the new hypotheses gaining traction? What are some companies working on these new ideas to watch in this space?

Jul 18, 2019 10:47 AM

There are a few companies to watch in the Alzheimer’s space, several of them public. Roche and Biogen both have very large Alzheimer’s programs, much of them focused on Amyloid. Lilly is still active in the area. In biotech, the big ones are probably Denali and Alector.

**Denali** was backed by ARCH and comprised of several executives known for their work at Genentech. They have several potential Alzheimer’s treatments in the early stages of clinical development, focusing on potential causes of neurodegeneration and the innate immune system in the brain.

**Alector** was founded by Arnon Rosenthal, who previously founded Rinat Biosciences. It is heavily focused on the brain’s immune system. It also has a program in frontotemporal dementia that is caused by a rare mutation; this is comparatively rare, accounting for about 5,000 patients in the US.

There’s also **Alzheon**. This is another beta-amyloid approach, with an oral drug. The company says it has learned from others’ mistakes. It was expected to IPO in the first half, but decided not to.

But many of the drugs that have been in testing have failed -- most recently the BACE inhibitor from Novartis and Amgen. Over the past 20 years, which is my whole career, only a single Alzheimer’s drug -- Namenda -- reached the market, and there were arguments over whether it was even effective. This is the toughest of tough spaces.
The past — and future — of Alzheimer’s research

https://stat.liveblog.pro/lb-stat/blogs/5d306a8bb89e0249a12110b...