Precision medicine offers a glimmer of hope for Alzheimer's disease

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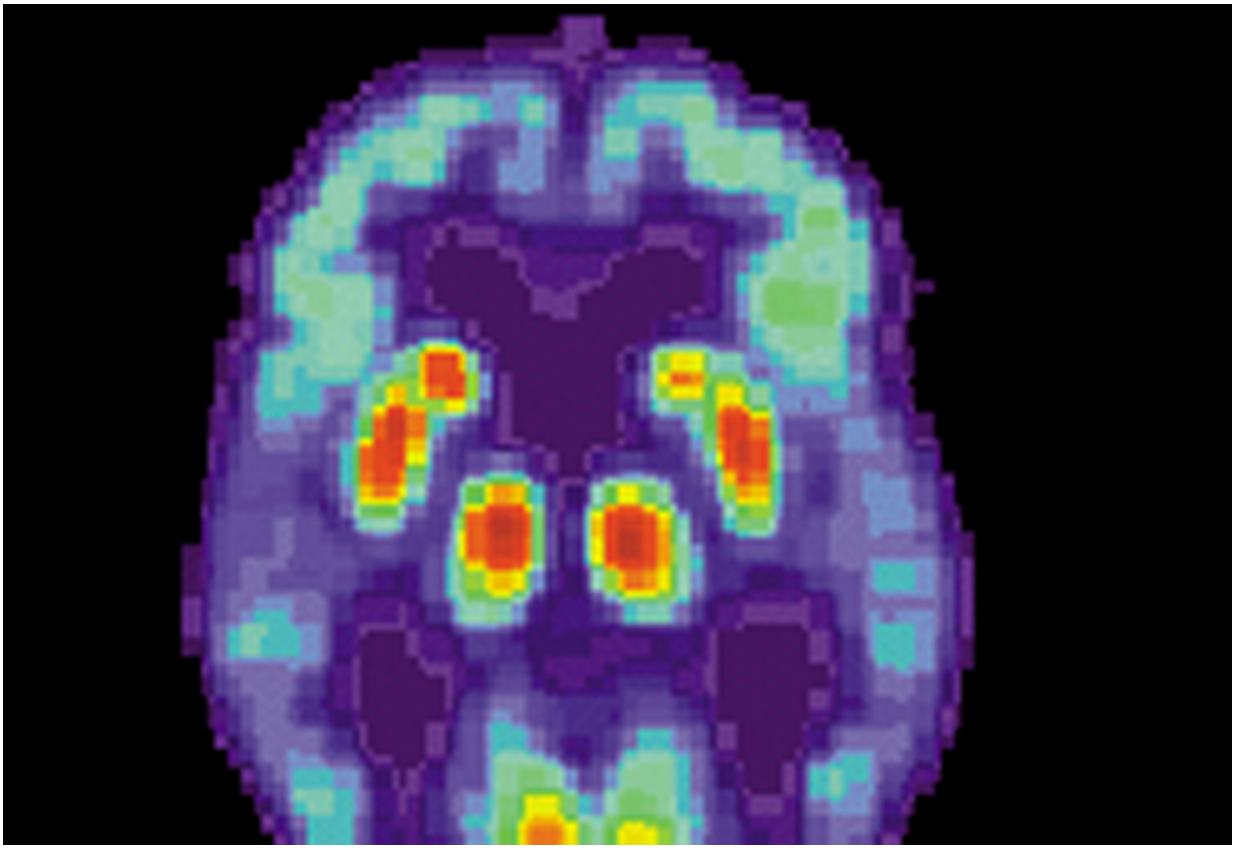

PET scan of a human brain with Alzheimer's disease. Credit: public domain

The decadeslong search for effective ways to treat or prevent Alzheimer's disease is littered with failures, leaving 5.7 million Americans already stricken with this form of dementia without a lifeline.

The rest of us are left to hope we won't be among the 1 in 10 over 65 who gets the devastating diagnosis.

But precision medicine—an approach that is changing the treatment of cancer and spawning targeted therapies for a wide range of diseases—may open new avenues for the treatment of Alzheimer's disease. And new ways to test experimental treatments promise to more quickly identify treatments that work, and perhaps the patients in whom they will work best.

This week, dementia specialists gathered at the Alzheimer's Association's International Conference in Chicago to assess the state of the field. And researchers gleaned some glimmers of real hope in both precision medicine and innovative trial designs to deliver new treatments for Alzheimer's disease.

These approaches raised expectations that at least two experimental drugs—one called BAN2401 and the other Anavex 2-73—might successfully treat some with Alzheimer's.

In the case of BAN2401, the successful preliminary finding of a trial that enrolled 856 patients with early Alzheimer's disease has breathed new life into a hypothesis that persists despite withering failures: that reducing clumps of proteins called amyloid plaques that accumulate in the brains of those with Alzheimer's might slow or reverse their symptoms of memory loss and cognitive confusion.

Using an innovative clinical trial design, the U.S. and Japanese companies developing BAN2401 found that over 18 months of treatment, patients who got the highest doses of the medication had dramatic reductions in amyloid plaque deposits in their brains. And compared with subjects who got a placebo, those who got the highest dose showed a 26 percent slowing of clinical decline after 18 months.

As the trial of BAN2401 progressed, its "adaptive design" ensured that when new subjects were recruited, they were more likely to be assigned to arms of the trial that showed the greatest promise. While considered controversial by some researchers, clinical trial designs that flex to seize upon promising preliminary findings have a high-level supporter in the Trump administration's Food and Drug Administration: Commissioner Scott Gottlieb.

"Alzheimer's disease trials need to evolve," said James A. Hendrix, director of global science initiatives at the Alzheimer's Association. "We need to try new things and learn from other diseases," he added, including fields such as cancer, where for select subsets of patients, new targeted therapies are delivering cures.

Distinguishing between likely responders and those not likely to be helped by a medication first, said Hendrix, "is an exciting new way to think about" new treatments for Alzheimer's. "Maybe one-size-fits-all is not the best approach," he added.

In a first-ever bid to apply the principles of precision medicine to Alzheimer's disease, researchers also reported this week on a small study of Alzheimer's patients who bear a few "actionable genetic variants." In these patients, they found, Anavex 2-73 appeared to slow and perhaps even reverse early cognitive decline.

The new findings emerged from a clinical trial designed to test the safety of Anavex 2-73, and it involved just 32 patients with mild to moderate Alzheimer's. So it's far too early to tout the success of this experimental drug.

But researchers built an extra step into their safety trial: sequencing the subjects' genomes. In doing so, they hoped to find genomic signatures in some patients that would make them more likely to respond positively to

the drug.

While the researchers combed through more than 33,000 genes, they had a pretty good picture of what molecular processes (or pathways) Anavex 2-73 worked on. So they knew what they were looking for: gene variations that were likely to interfere with the actions of Anavex 2-73 and make treatment unsuccessful. They found two such genetic variants, present in about one-fifth of humans.

When researchers from Anavex narrowed the subject pool to just those patients whose genetic makeup was compatible with its mode of action, they found that subjects who got the medication for 57 weeks experienced "clinically meaningful" improvements in their ability to reason, remember and carry on daily activities.

A larger new trial on subjects with Alzheimer's is set to begin in Australia and North America. The experimental medication is also being tested as a possible treatment for dementia associated with Parkinson's disease, for Rett syndrome and for Fragile X syndrome.

The idea that a medication to treat Alzheimer's disease might work well in some dementia patients and not as well in others is consistent with a growing sense, first, that Alzheimer's may be many different diseases. But it also fits with the notion that genetic factors—acting alone or collectively—predispose some to Alzheimer's while protecting others.

In precision medicine, sometimes called personalized medicine, researchers work to identify the genetic factors that drive or contribute to a disease and build medicine that targets the downstream effects of those miscreant genes. Then, they use genomic sequencing technologies to identify just those patients who bear the distinctive genetic signatures their drug works on. More often than not, these drugs are costly, and they don't work on everyone. But when the right patients get the right

medicine at the right time, treatments will be more effective and have fewer side effects.

"If you include a biomarker, which can be detected in a matter of hours or days by a swab test, then you can enrich a study—enroll just the subjects most likely to respond—and of course, improve the chances of success," said Christopher Missling, a founding director of Anavex Life Sciences Corp.

Such new approaches to treating dementia could turn the tide in the discouraging search for Alzheimer's treatments, said Dr. Deepak Bhatt, an expert on adaptive trial designs and precision medicine.

"Identifying which patients might benefit from a novel therapy using biomarkers or genetics will likely be a big part of how medicine is individualized in the future—so-called precision medicine," said Bhatt, who directs interventional cardiovascular programs at Brigham and Women's Hospital in Boston.

"This approach may be especially well suited for therapies that might have side effects or are expensive. While further confirmatory studies are needed for this particular Alzheimer's drug before clinical use, the potential of personalizing care for such a devastating disease is exciting. "