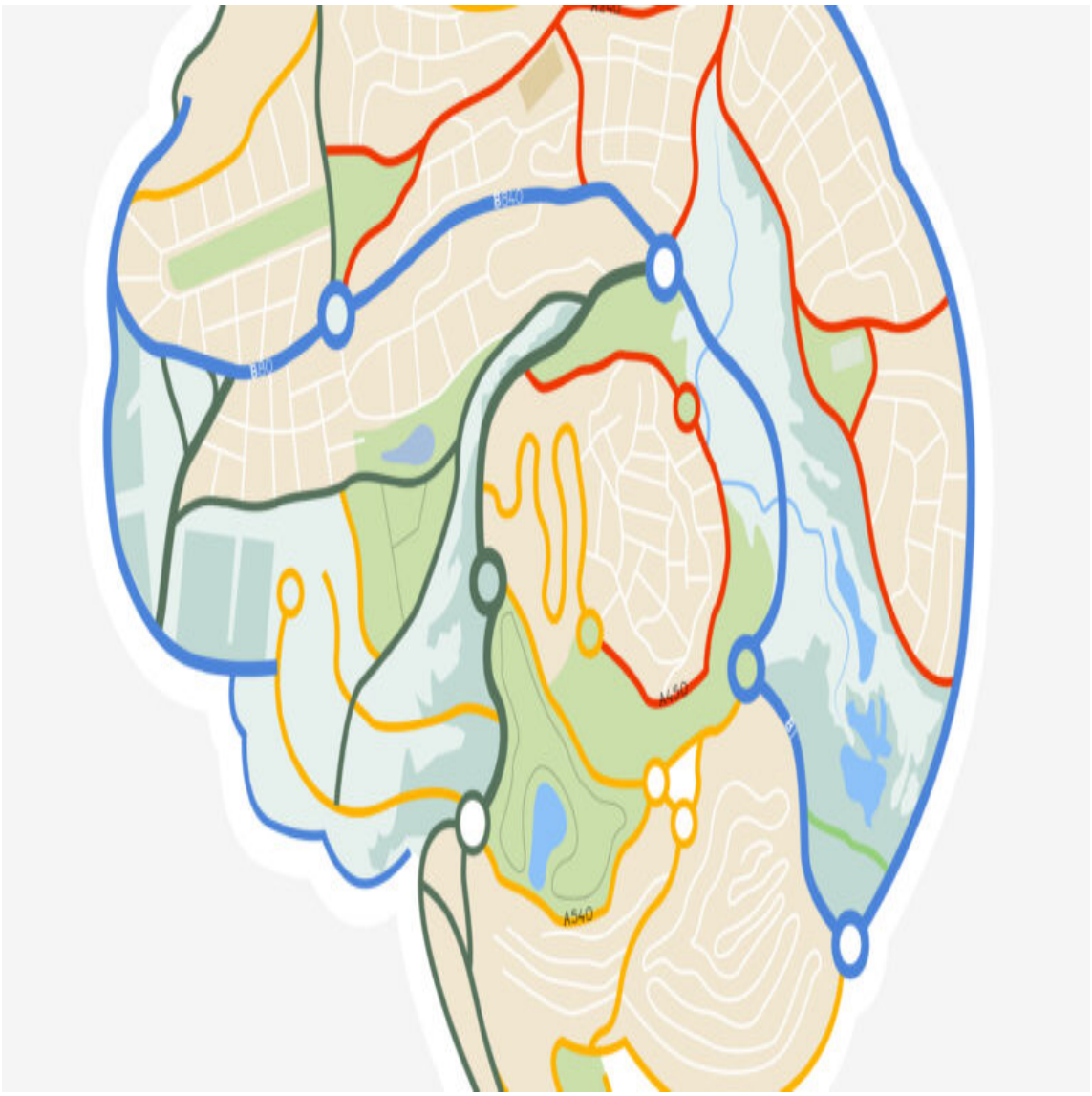
Aduhelm's accelerated approval offers a promising roadmap for rare neurological diseases

By Emil D. KakkisJuly 7, 2021



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The FDA's decision to grant accelerated approval[2] to Biogen's aducanumab (Aduhelm) for the treatment of Alzheimer's disease was a difficult and bold one that people with the disease, their families, and other drug developers should be applauding.

When it comes to making new therapies for complex, difficult-to-treat diseases, history has shown that progress can't be made without taking a first — often controversial — step. Without the FDA's accelerated approval program[3] and novel first treatments based on new and imperfect biomarker endpoints, HIV would not be a controllable disease today, and we might not have such a flourishing clinical research ecosystem in oncology.

In the early 1990s, the drug development and regulatory landscape for new AIDS therapies was bleak: no new drugs had been approved since the first antiretroviral therapy, zidovudine (also known as AZT) in 1987. It took the work of ACT UP and other passionate AIDS activists to spur the FDA to develop regulations in 1992 allowing for a surrogate biomarker to support new drug approvals rather than relying on opportunistic infection and death.

That first biomarker, the CD4 cell count[4], was imperfect, but it led to the rapid availability of more effective therapies. The concurrent development of an even better biomarker, viral load[5], then led to even more potent drug combinations that could knock down the infection more thoroughly. They changed the future.

Opening the door to the use of a biomarker for accelerated approval led to significant investment in new and better drug targets and alternative mechanisms of action, so much so that 29 new and improved therapies or combination therapies[7] were approved within 16 years, effectively turning HIV into a chronic disease. Importantly, this use of the viral load biomarker works well early in the disease course, before there are clear clinical symptoms, and so is better suited to developing an effective treatment to slow, or even stop, the disease from progressing. The same could be true for Alzheimer's disease, for which the prevention of neurocognitive decline is the goal and it may take many years before clinical symptoms can be observed and measured, which is required to demonstrate efficacy in a conventional development pathway reliant upon clinical outcomes.

Few who fought with fervor and sanctimony against biomarker-based approvals for HIV therapies at that time will speak up or admit their error today. The advancement of the science occurred only through those first imperfect and uncertain steps and

over the objection of those who claimed to protect the public and warned of harm to drug development, concerns that proved unwarranted.

The two most productive areas in biotechnology today are treatments for viral infectious diseases and cancer, both of which are precisely the two areas where the use of biomarkers or surrogate endpoints for accelerated approvals are widely employed. This is no accident.

The Alzheimer's drug development and regulatory landscape has likewise been a bleak landscape for years. The accelerated approval of Aduhelm is likely to rejuvenate this depleted area, inevitably leading down the long walk to better and better therapies as well as better ways to measure this disease.

There are many diseases for which surrogate biomarkers may be the only route to developing new drugs. Like Alzheimer's, rare neurodegenerative genetic diseases including Sanfilippo syndrome[9] (also known as mucopolysaccharidosis type III) and Niemann Pick disease type C make it particularly challenging to apply the normal rules of drug development. The progression of these diseases varies from patient to patient, who show mixed degrees of irreversibility. It's nearly impossible to properly power a randomized, controlled trial of reasonable size in a reasonable time frame for a disease with variable progression over many years, especially when most patients are diagnosed in late stages and are already well down the path of irreversible disease progression.

In rare diseases like these, where the pathology is well understood, the science behind using surrogate biomarkers is much clearer than it is for using them even in Alzheimer's disease, as the FDA did with the accelerated approval of Aduhelm.

Using the underlying genetics of rare diseases to identify biomarkers that are reasonably likely to predict the benefit of novel therapies should make it possible to rely on these biomarkers for accelerated approval. My colleagues and I have advocated for greater access to appropriate use of this pathway for more rare disease treatments that might not be developed otherwise and proposed a scientific framework[10] in 2015 for qualifying and assessing biomarkers as primary endpoints.

Sanfilippo syndrome is an interesting illustration. It is akin to Alzheimer's disease in children, based on a number of features. Children with Sanfilippo syndrome are born with a genetic abnormality so their bodies are unable to breakdown heparan sulfate, a natural cellular product that needs to be recycled. Accumulation of an excess of heparan sulfate is toxic to the body and the brain. Almost everyone born with this syndrome dies before adulthood. There is no approved drug for Sanfilippo syndrome, nor is there any approved surrogate biomarker. If use of the heparan sulfate level in cerebrospinal fluid was to be recognized as a biomarker that reflects the underlying disease activity, it could accelerate a number of therapeutic programs[11] that are now at risk for never being approved.

As has been seen with HIV and cancer, applying the accelerated approval pathway in urgent rare disease research areas could significantly encourage and support innovation. A review of rare disease indications[14] suggests that expanded use of the accelerated approval program could reduce costs of drug development up to 62% and accelerate the time frame for the first and subsequent therapy approvals.

The CD4 cell count biomarker initially used to evaluate therapies for HIV did not have perfect correlation or predictive value of efficacy. Yet the science at the time was deemed reasonably likely to predict effectiveness and thus began the stepwise progression of medical evolution toward better and better treatments. That standard needs to be applied to supporting new treatments for rare neurological diseases, where the timing is especially critical and where even greater confidence exists in the correlation between surrogate biomarkers and clinical outcomes than in Alzheimer's disease.

The biomedical research community would not be where it is today without striving for progress over perfection. The imperfect, uncertain first steps of accelerated approval are needed to walk the path to optimal treatment. I appreciate the FDA taking this needed step for Alzheimer's patients.

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