

Aducanumab: Panacea or Risk for Adults with Down Syndrome

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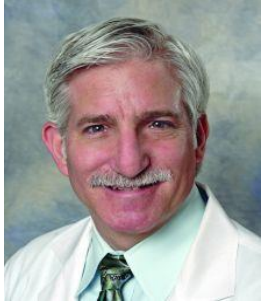
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National Task Group on Intellectual Disabilities
and Dementia Practices

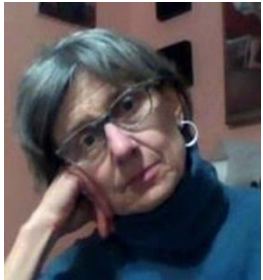
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About us



Seth M. Keller, M.D. is co-president of the US National Task Group on Intellectual Disabilities and Dementia Practices, Past President of the AADMD, Chair of the Adult Intellectual and Developmental Disabilities Section of the American Academy of Neurology, member of the Healthcare Board Arc of NJ, and a Consulting Neurologist for New Jersey State ICF/IDD Centers.



Kathryn Service, RN, MS, FNP-BC, CDDN had worked as an RN/NP for close to 40 years with the Massachusetts Department of Developmental Services. In addition to ‘hands-on’ clinical support, she has worked together with and presented to people with ID and their families and direct support professionals and now still consults independently on matters on dementia, aging and end-of-life care. She is an officer of the National Task Group on Dementia and Intellectual Disabilities.



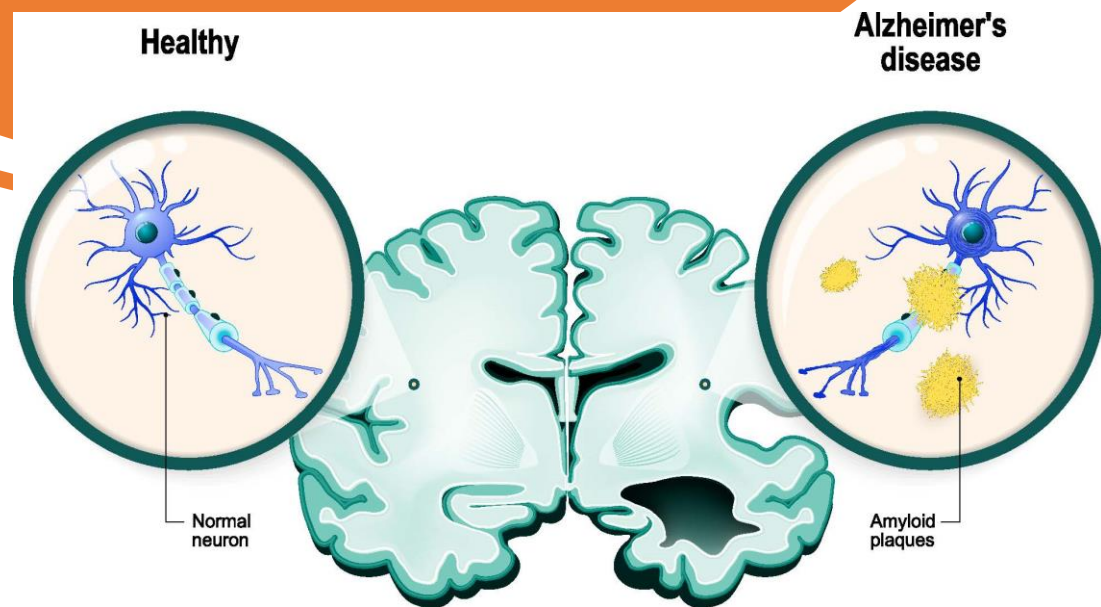
Matthew P. Janicki, Ph.D. is co-president of the US National Task Group on Intellectual Disabilities and Dementia Practices, as well as an associate professor in the Department of Disability and Human Development at the University of Illinois at Chicago and a member of the federal Advisory Council on Alzheimer’s Research, Care, and Services. Formerly, he was director for aging and special populations for the New York State Office for People with Developmental Disabilities.

The Basics...

- What is aducanumab? What is Aduhelm?
- How the medication works?
- What is the controversy in general?
 - How was it approved?
 - Does it work?
 - Why does it cost so much?
 - Who can get it?
- What does all this mean to us (in the ID field)?
 - Now?
 - In the future?



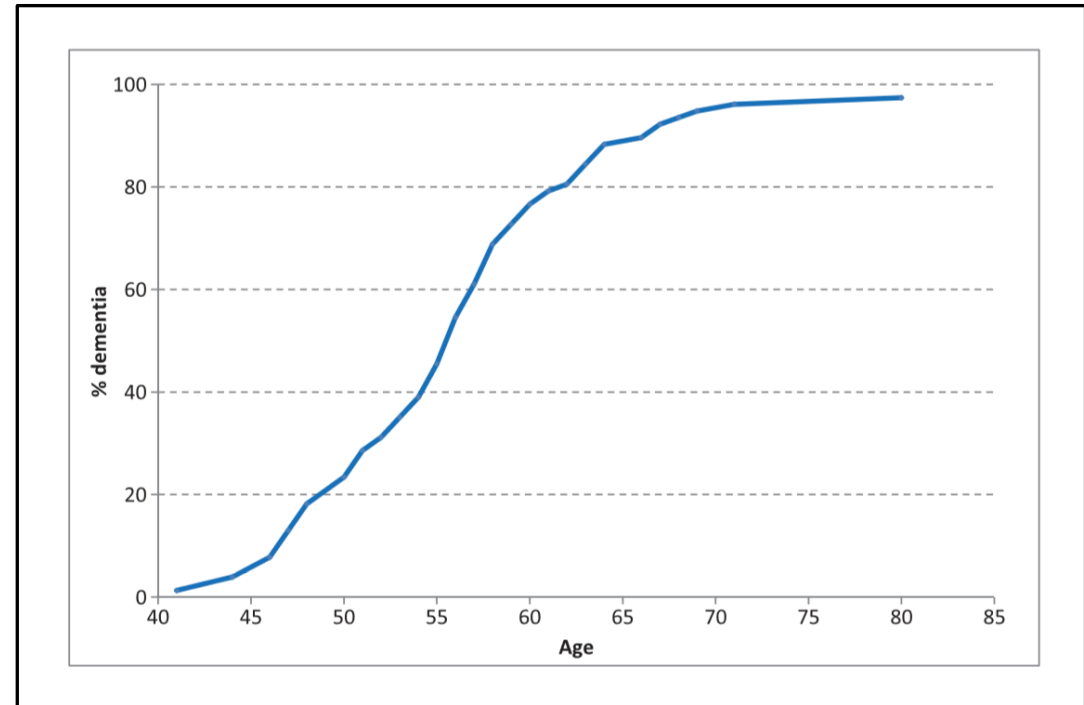
...and now for something completely different



- **What is the difference between Alzheimer's disease and dementia?**
 - Alzheimer's disease is a disease of the brain which reduces a person's ability to think, function, and remain independent in the community
 - There are various theories about what causes this disease – one is the amyloid hypothesis, which is based on the belief that a build up of the beta amyloid protein in brain cells eventually cause the cells not to function
 - It is believed that Alzheimer's disease originates some 20 or so years before there is evidence of dementia
- **What is dementia?**
 - Dementia is a common term for memory losses, confusion, and decline in cognitive and behavioral function usually associated with Alzheimer's disease or other causes where the brain is affected
 - Other causes are brain changes due to strokes (due to blood vessels bursts or blood clots) or other diseases of the brain
 - Most dementia occurs in older age, with symptoms usually first evident in the 70s and with increasing incidence with progressive age

Alzheimer's Disease in Down Syndrome

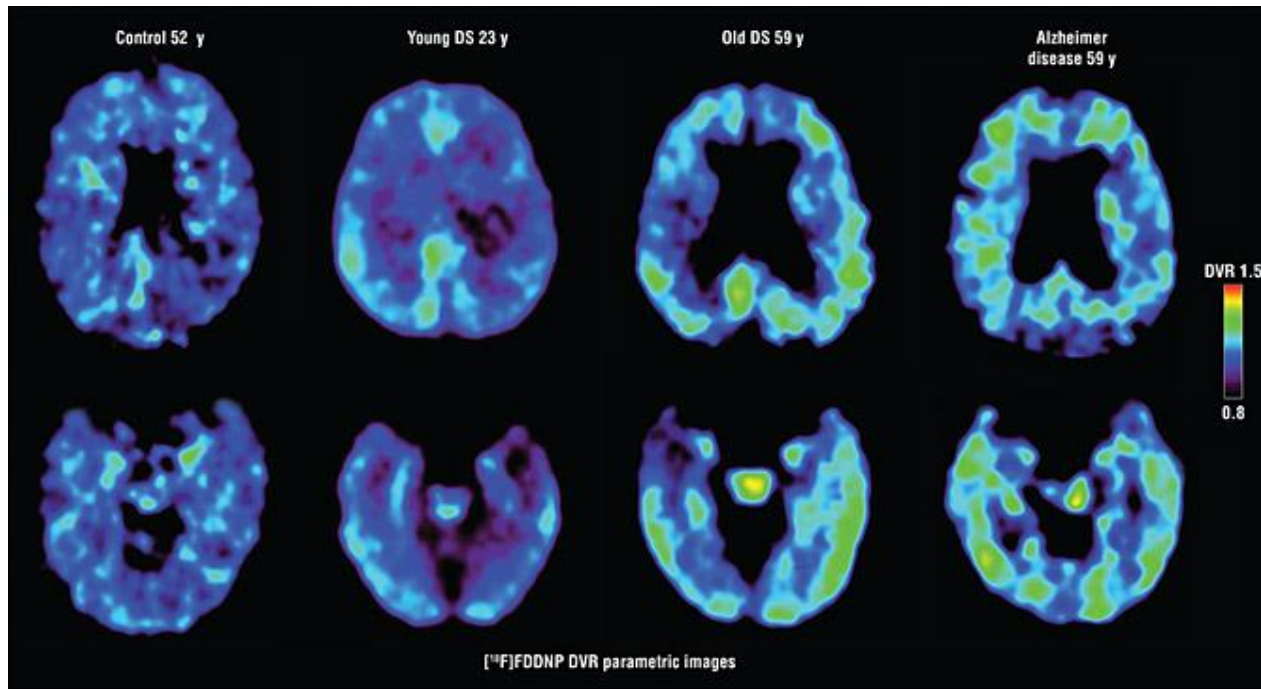
- High prevalence of early onset AD due to having extra copy of chromosome 21 leading to accumulation of beta amyloid protein, tau protein, and neurodegeneration
- People with Down syndrome who develop Alzheimer's disease live, on average, 4-10 years from first symptoms; median 7 years
- Rapid decline can occur



Percentage of people with Down syndrome who develop dementia at different ages:

30's	2%
40's	10-15%
50's	20-50%
60's	60-90%

McCarron et al., (2017). A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *Journal of Intellectual Disability Research*, Sep;61(9):843-852

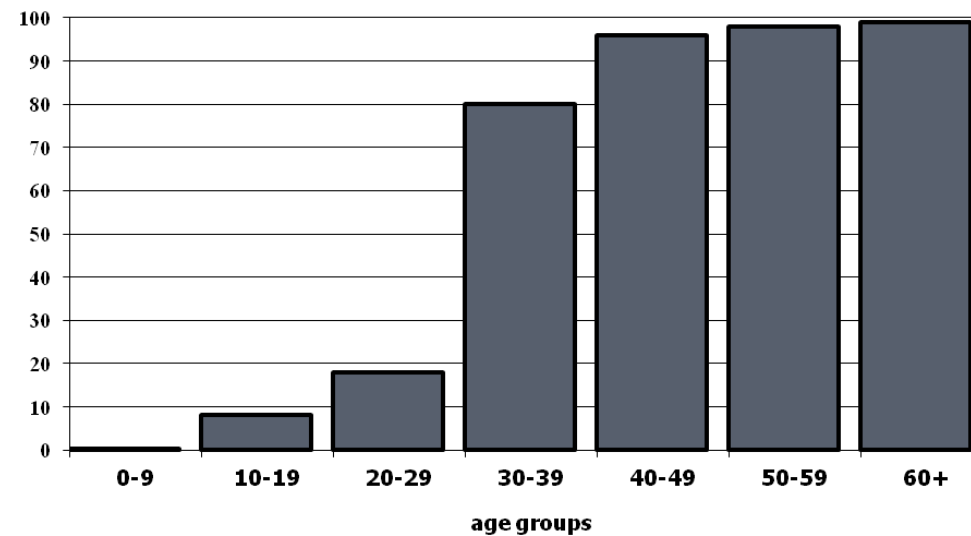


Representative amyloid scans in Down syndrome and Alzheimer's disease

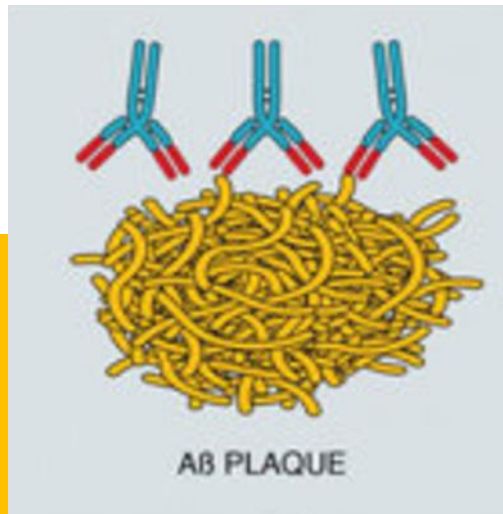
Nelson, L. D. et al. Arch Neurol., 2011; 68; 768-774.

Percent persons with Down syndrome showing evidence of neurofibrillary tangles (NFT) and senile plaques (SP) at autopsy

Mann, D.M.A. (1993). Association between Alzheimer disease and Down syndrome: Neuropathological observations. In J.M. Berg, H. Karlinsky, & A.J. Holland (Eds.) *Alzheimer disease and Down syndrome and their relationship* (pp. 71-92). Oxford University Press



What is aducanumab?



"Aducanumab (Aduhelm) is an antibody that targets amyloid-beta. The antibody preferentially binds to the aggregated amyloid-beta. This is because it targets an epitope that is not normally accessible in the amyloid-beta monomer. Through this interaction, Aduhelm could reduce the number of amyloid plaques present in the brain, potentially slowing neurodegeneration and disease progression."

[source: Alzheimer's News Today]

Aducanumab is the generic name for this specific medication

Aduhelm is Biogen's trade name for the drug

What are the controversies?

- **How was it approved?**

- The FDA used its Accelerated Approval Program, which allows for earlier approval of drugs that treat serious conditions and that fill an unmet medical need based on a 'surrogate endpoint'. A 'surrogate endpoint' is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit – but is not itself a measure of clinical benefit.

- **Does it work?**

- Aducanumab is an antibody that targets amyloid-beta. The antibody preferentially binds to the aggregated amyloid-beta and via this interaction, aducanumab could reduce the number of amyloid plaques present in the brain, potentially slowing neurodegeneration and disease progression. While the Biogen clinical trials showed a lessening of amyloid, the data were unclear whether there was any cognitive benefit.

- **What are the risks?**

- Changes are seen on the MRI [*magnetic resonance imaging*] including brain swelling and small areas of bleeding during the treatments. Headaches and confusion can occur

- **Why does it cost so much?**

- Much has been made of the \$56,000 annual cost of treating someone with Aduhelm; this is only the cost of the medication and does not include the costs of the pre-prescription assessment to determine whether Alzheimer's disease is present, nor does it include the associated peri-treatment costs for monitoring the drug's effects. The cost was set by Biogen and is being investigated by a Congressional committee.

- **Who can get it?**

- The FDA announced on July 8th, that its current use was limited to adults diagnosed with MCI or early-stage dementia associated with Alzheimer's disease. While the FDA was silent on patient appropriateness beyond these two diagnostic categories, the Expert Panel noted that it was NOT appropriate for use with adults with Down syndrome at this time

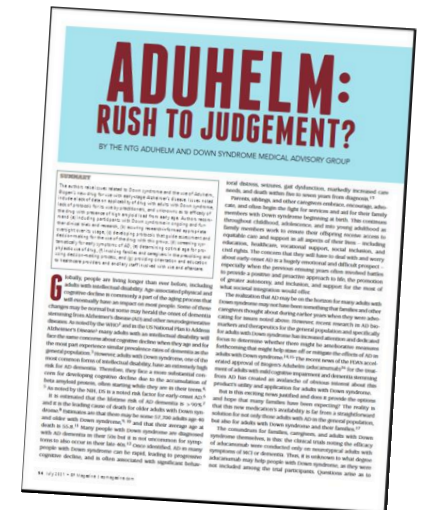
What happened after June 7th?

The NTG used its Scientific and Medical Advisory Panels to organize a cross-organizational effort to examine Biogen's new medication and to determine its use and applications to people with intellectual disability – specifically Down syndrome

The resulted in the creation of the special 'MAG' – the Aduhelm and Down Syndrome Medical Advisory Group

The MAG created a cross-cutting statement and got sign-ons from numerous ID/DD and DS organizations

The statement appeared quickly in the June issue of *Exceptional Parent* and was distributed widely across the world





Recommendations of the MAG

- Advance protocols for assessment and use agreed upon by an expert panel which should provide cautioned guidance for practitioners considering prescribing aducanumab in adults with DS (and other intellectual disabilities).
- A well-defined screening process should be in place for determining the stage of AD, as well as a recognized and approved process for the therapeutic use of aducanumab that all healthcare providers would follow to ensure safety and ability to determine efficacy in adults with DS.
- A commitment be made for early detection and screening by the nation's disability services provider network and state regulatory authorities to pick up on early symptoms at a stage when the use of aducanumab may be effective.
- Adults with DS, families, and other caregivers be part of the decision-making process for drug use and while the prescribed medical care is being provided.
- An orientation and education package be organized to help educate healthcare providers and any ancillary staff involved in the clinical use of this therapeutic.

...and now for
something
completely
different

- **How would I know if an adult with an intellectual disability has dementia?**
 - For adults with intellectual disability ... look for symptoms generally in the late 60s or 70s
 - Symptoms would include forgetfulness, confusion, general cognitive and functional decline – changes from previous levels
- **How would I know if an adult with Down syndrome has dementia?**
 - For adults with Down syndrome... look for symptoms generally in the early 50s
 - Symptoms would include a change in personality, forgetfulness, confusion, and general cognitive and functional decline
- **What should I do?**
 - Ask one of your clinicians (a physician, nurse, psychologist, behaviorist) to check with staff about noticeable changes, preferably using a screening tool (like the NTG-EDSD)
 - You can also have a caregiver or family member complete the screening tool (if they live with the adult)
 - Organize a clinical team meeting to discuss the results and if symptoms seem serious, then refer to a qualified clinician to undertake a formal assessment and possibly do a diagnostic evaluation

You can find the **NTG-EDSD** at www.the-ntg.org/ntg-edsd

Expert Panel statements re: Down syndrome

- “Individuals with Down syndrome essentially uniformly develop brain amyloid plaques and often have symptoms of dementia in. The presence of amyloid plaques in Down syndrome suggests that treatment with aducanumab may be beneficial. There are many differences between Down syndrome and late onset AD, and the [Cummings et al.] Expert Panel *recommends against treating Down syndrome patients with aducanumab until more data are available.*”
- “Patients with Down syndrome that meet all the other criteria for treatment with aducanumab may become treatment-eligible when additional studies have been conducted and additional data are available.”

The
conundrum
for families,
caregivers,
and adults
with DS, is
this...

... the clinical trials noting the efficacy of aducanumab were conducted only on neurotypical adults with symptoms of MCI or early dementia, so that any applications of aducanumab with adults with DS would be off-label use ...

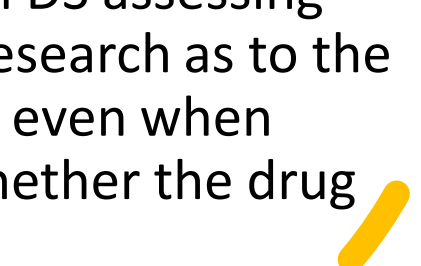


At this point, we do not know to what degree aducanumab may help people with DS, as they were not among the initial trial participants...

Questions arise as to **whether aducanumab's impact** on brain amyloid, associated vascular complications, doses used and its titration, **may also be similar in people with DS.**

Furthermore, **cognitive benefits have yet to be clearly demonstrated** with aducanumab and it is **still unknown whether** the *MRI-related changes* [including amyloid related imaging abnormalities (ARIA)] *and other possible side effects* (such as brain swelling and micro-hemorrhages) **would also apply to adults with DS.**

Without **safety studies** targeting adults with DS assessing the possible adverse outcomes, as well as research as to the maintenance benefit of cognitive functions, even when amyloid is reduced, questions arise as to whether the drug can be beneficial to adults with DS.



A bag full of issues... Part A (drug)

- What may be any possible **adverse effects** from the drug?
- How it may be best administered to adults who may not **tolerate monthly** hospital visits?
- What will be the **diagnostic process** for determining eligibility for atypical adults?
- What may be the **optimal dosage variance** for adults with Down syndrome compared to other adults?
- What may be the **measures of drug efficacy** for most adults with Down syndrome and within what timelines given the syndrome-specific compression of the effects of Alzheimer's?
- What point will adults with Down syndrome be **eligible for receipt** of the drug (that is, will it be able to be used as a prophylactic given the inherent risk for Alzheimer's among adults with Down syndrome)?
- Will there be **time limits** on prescriptions for Aduhelm treatments once dementia is determined to be advancing?

A bag full of issues... Part B (financial)

- Will **insurers** consider adults with Down syndrome eligible for coverage?
- Whether there will be **financial aid** for families due to the annual cost of the drug?
- What **equity considerations** will be supported by DHHS and the Courts?
- How will **ancillary costs** (pre-prescription PET scans and assessments and post-procedure associated surveillance) be covered for families of adults with Down syndrome?
- Will **state developmental disabilities agencies** be required to initiate referrals for assessments and provide coverage for treatment for adults in their services?
- What will be the **financial implications** for provider agencies?

A bag full of issues... Part C (misc.)

- Will there be funding to support **specialized intellectual disability assessment centers** equipped with infusion chairs and able to provide regular M.R.I. scans to track any potential side effects? How would these centers be set up?
 - Will there be **specialized training** of hospital personnel at clinics with infusion chairs about the special needs of adults with Down syndrome? What should it be?
 - Will centers with infusion chairs and other supports set **triage parameters** on the type and number of adults they will treat?
-
- What will be the parameters of **informed consent** by adults with Down syndrome to obtain use of the drug?
 - How will **family support groups** be funded and managed for families whose off-springs with Down syndrome are participating in Aduhelm treatments?
 - What has to be done to include adults with Down syndrome in any subsequent **clinical trials**?

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something
completely
different

- **Where can I get more information about the use of this medication locally?**
 - Usually, a local hospital or memory clinic will have specialists who see patients diagnosed with Alzheimer's disease
 - Check with them about whether they may be treating patients with disabilities and what has been their experience
 - Remember, that the medication has not been recommended for use by adults with Down syndrome
- **What should I advise parents/caregivers if they ask me for advice?**
 - For adults with Down syndrome... tell them that the medication has not yet been approved for use by adults with Down syndrome
 - Safety studies to be undertaken will help us better know whether there are any serious adverse reactions and whether the medication is effective in mitigating cognitive symptoms
 - For adults with other intellectual disability... tell them that no data exist as to whether the medication might be helpful at this time

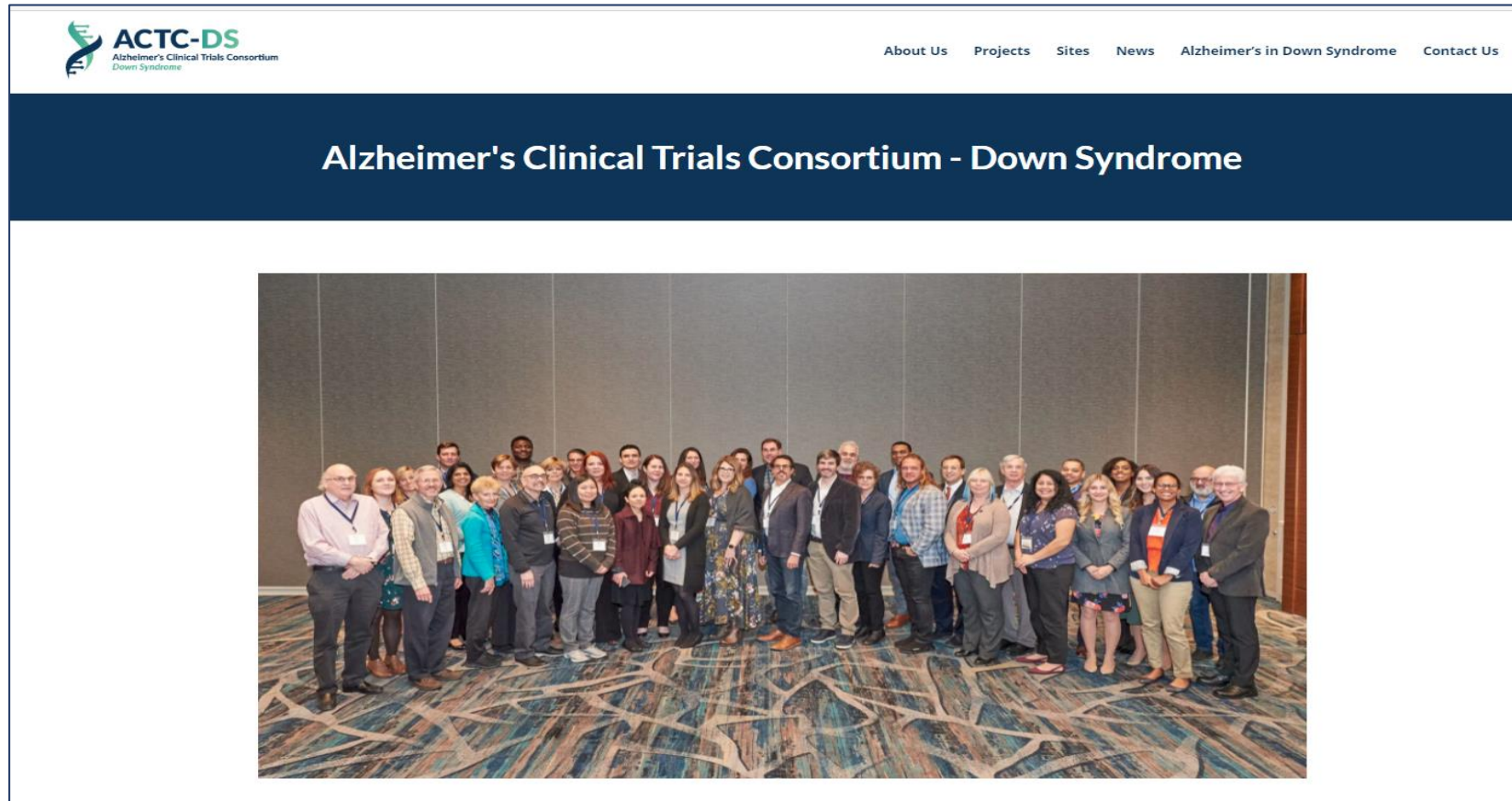
Actions affecting agencies...

- ✓ Adapting and using protocols that guide assessment and decision-making for the use of the drug with this group
- ✓ Undertaking systematic screening for early symptoms of Alzheimer's disease
- ✓ Benefiting from research determining optimal age for prophylactic use of drug
- ✓ Undertaking behavioral mitigation practices to help adaptation to monthly drug infusion
- ✓ Involving families and caregivers in the prescribing and decision-making process
- ✓ Providing orientation and education to healthcare providers and ancillary staff involved with use and aftercare

Points to consider...

- **Training** – Most healthcare providers are not trained in how to assess and diagnose Alzheimer’s disease in adults with intellectual disability (including adults with Down syndrome)
- **Assessment** – During the pre-prescription assessment phase, specific challenges may arise in communicating with the patient, parsing memory loss from premorbid intellectual functioning, and mitigating examination intolerance
- **Knowledge** – Most memory centers are bereft of staff skilled in interviewing and assessing persons with pre-existing cognitive limitations and who also may be uninformed as to the best courses of health and social care for adults with Down syndrome
- **Equity** – As protocols for the use of aducanumab are implemented, adults with Down syndrome must be provided with equitable care and support once diagnosed with Alzheimer’s disease

Updates... ACTC-DS



The NIH-funded Alzheimer's Clinical Trials Consortium – Down Syndrome (ACTC-DS) network is assembling an international collaborative to address some of these questions by running safety studies on persons with Down syndrome

Updates... CMS

MCD
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National Coverage Analysis (NCA) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)

COMMENT

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Issue

Alzheimer's disease is a progressive, currently irreversible brain disorder that slowly degrades memory, cognitive function, and ability to carry out tasks of daily living. It is the most common cause of dementia among older adults. In Alzheimer's disease, brain cell functioning is disrupted resulting in failure of brain cells to communicate with one another, leading eventually to cell death. Although many molecular and cellular changes are associated with the onset and progression of Alzheimer's disease, aggregates of beta amyloid are thought to play an important role in its pathophysiology.

On June 7, 2021, the Food and Drug Administration (FDA) approved, using accelerated approval, aducanumab (brand name Aduhelm™) with an indication for the treatment of Alzheimer's disease. Aducanumab is a monoclonal antibody directed against amyloid beta to reduce amyloid accumulations.

[National Coverage Analysis \(NCA\) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease \(CAG-00460N\) \(cms.gov\)](https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet-for-monoclonal-antibodies-directed-against-amyloid-for-the-treatment-of-alzheimer-s-disease-cag-00460n)

Biogen Medical Information Notice RE ADUHELM™ (aducanumab-avwa): Use in Persons with Down Syndrome (Trisomy 21) [\(8/4/21\)](#)

Biogen's notice is offered as an educational resource for healthcare providers in response to an unsolicited request by Dr. Seth Keller, Co-President of the NTG. **The notice indicates that aducanumab-avwa has not been studied in persons with Down Syndrome associated Alzheimer's disease (DSAD), and there are no data on the efficacy and safety in this population; therefore, it is not indicated for use in persons with Down syndrome.**

The notice cites the work of *Cummings et al. (2021)* which acknowledges that there are many differences between Down syndrome and late onset AD and as such, it is recommended against treating persons with Down syndrome with aducanumab-avwa until more data are available. According to *Cummings et al.*, persons with Down syndrome may eventually become eligible for treatment after additional studies have been conducted and additional data are accrued for this group of individuals. It also cites various sources, including the NTG, recommending the generation of more applicability and use protocols.



The image is a screenshot of a Biogen press release page. At the top, the Biogen logo is on the left, and navigation links for 'OVERVIEW', 'NEWSROOM', 'EVENTS & PRESENTATIONS', 'FINANCIALS', 'STOCK INFORMATION', and 'CORPORATE GO' are on the right. Below the navigation is a decorative header with a blue and green abstract pattern. The main content area is white and contains the following text: 'Biogen and Eisai Announce Design of ADUHELM ICARE AD-US Study, the First Real-World Observational Phase 4 Study in Alzheimer's Disease at AAIC 2021'. Below this, in smaller blue text, it says 'JULY 29, 2021 • INVESTOR RELATIONS'.

[Biogen and Eisai announced design of ADUHELM ICARE AD-US Study, the first real-world observational phase 4 study in Alzheimer's disease, at AAIC 2021 | Biogen](#)

For more information...

<https://www.the-ntg.org/aduhelm-information>